7/7/02 60249

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Rao Tumma Examiner #: 65630 Date: 2/13/02
Art Unit: 1623 Phone Number 308-0732 Serial Number: 09/421,545
Mail Box and Bldg/Room Location: 8919 7AN Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): _____

Earliest Priority Filing Date: _____

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

JAN

RECEIVED
FEB 13 2002
CHEM/BIO (STIC)

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 - 703-308-4498
jan.delaval@uspto.gov

****

STAFF USE ONLY

Searcher: Jan
Searcher Phone #: 4498
Searcher Location:
Date Searcher Picked Up: 3/1/02
Date Completed: 3/1/02
Searcher Prep & Review Time:
Clerical Prep Time: 15
Online Time: +110

Type of Search

NA Sequence (#)
AA Sequence (#)
Structure (#)
Bibliographic ✓
Litigation
Fulltext
Patent Family
Other

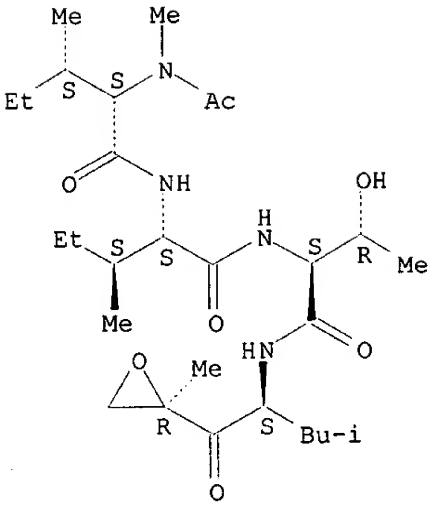
Vendors and cost where applicable

STN ✓
Dialog
Questel/Orbit
Dr.Link
Lexis/Nexis
Sequence Systems
WWW/Internet
Other (specify)

PTO-1590 (8-01)

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 16:44:45 ON 01 MAR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 American Chemical Society (ACS)

STRUCTURE FILE UPDATES:   28 FEB 2002  HIGHEST RN 397241-73-5
DICTIONARY FILE UPDATES:  28 FEB 2002  HIGHEST RN 397241-73-5

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the
CAS Registry Numbers that were added to the H/Z/CA/CAplus files between
12/27/01 and 1/23/02.  Use of the P indicator in online and SDI searches
during this period, either directly appended to a CAS Registry Number
or by qualifying an L-number with /P, may have yielded incomplete results.
As of 1/23/02, the situation has been resolved.  Also, note that searches
conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files
incorporating CAS Registry Numbers with the P indicator between 12/27/01
and 1/23/02, are encouraged to re-run these strategies.  Contact the
CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698,
worldwide, or send an e-mail to help@cas.org for further assistance or to
receive a credit for any duplicate searches.

=> d ide can tot l1

L1   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2002 ACS
RN   134381-21-8  REGISTRY
CN   L-Threoninamide, N-acetyl-N-methyl-L-isoleucyl-L-isoleucyl-N-[(1S)-3-
     methyl-1-[[(2R)-2-methyloxiranyl]carbonyl]butyl]- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   BU 4061T
CN   Epoxomicin
FS   STEREOSEARCH
MF   C28 H50 N4 O7
SR   CA
LC   STN Files:   AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT,
       CAPLUS, CEN, CHEMCATS, CSCHEM, EMBASE, MEDLINE, SYNTHLINE, TOXCENTER,
       TOXLIT, USPATFULL

Absolute stereochemistry.
```

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

12 REFERENCES IN FILE CA (1967 TO DATE)
12 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:254547

REFERENCE 2: 135:42638

REFERENCE 3: 134:331618

REFERENCE 4: 134:128358

REFERENCE 5: 133:148873

REFERENCE 6: 132:216387

REFERENCE 7: 132:160826

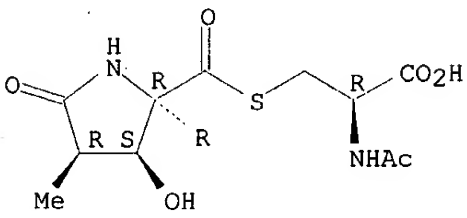
REFERENCE 8: 132:89911

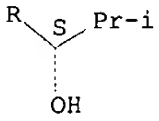
REFERENCE 9: 131:306864

REFERENCE 10: 131:299679

L1 ANSWER 2 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN **133343-34-7** REGISTRY
CN L-Cysteine, N-acetyl-, (2R,3S,4R)-3-hydroxy-2-[(1S)-1-hydroxy-2-methylpropyl]-4-methyl-5-oxo-2-pyrrolidinecarboxylate (ester) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Cysteine, N-acetyl-, 3-hydroxy-2-(1-hydroxy-2-methylpropyl)-4-methyl-5-oxo-2-pyrrolidinecarboxylate (ester), [2R-[2.alpha.,2(S*),3.alpha.,4.alpha.]]-
OTHER NAMES:
CN (+)-Lactacystin
CN Lactacystin
FS STEREOSEARCH
MF C15 H24 N2 O7 S
CI COM
SR CA
LC STN Files: AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMINFORMRX, CSCHEM, EMBASE, MEDLINE, PHAR, PROMT, SYNTHLINE, TOXCENTER, TOXLIT, USPAT2, USPATFULL

Absolute stereochemistry. Rotation (+).





PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

173 REFERENCES IN FILE CA (1967 TO DATE)
13 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
176 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:128735

REFERENCE 2: 136:116599

REFERENCE 3: 136:79790

REFERENCE 4: 136:67345

REFERENCE 5: 136:63726

REFERENCE 6: 136:31378

REFERENCE 7: 136:15055

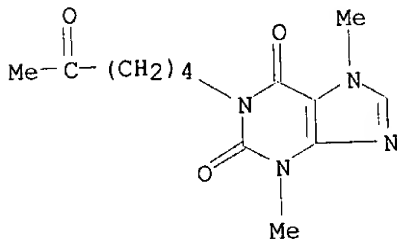
REFERENCE 8: 135:352382

REFERENCE 9: 135:344727

REFERENCE 10: 135:327142

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2002 ACS
RN **6493-05-6** REGISTRY
CN 1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Theobromine, 1-(5-oxohexyl)- (7CI, 8CI)
OTHER NAMES:
CN 1-(5-Oxohexyl)-3,7-dimethylxanthine
CN 1-(5-Oxohexyl)theobromine
CN 3,7-Dihydro-3,7-dimethyl-1-(5-oxohexyl)-1H-purine-2,6-dione
CN 3,7-Dimethyl-1-(5-oxohexyl)-1H,3H-purin-2,6-dione
CN 3,7-Dimethyl-1-(5-oxohexyl)xanthine
CN Agapurin Retard
CN BL 191
CN Dimethyloxohexylxanthine
CN Oxpentifylline
CN Pentoxifyllin
CN Pentoxifylline

CN Pentoxiphyllin
CN Pentoxiphylline
CN Pentoxyfilline
CN Pentoxyphyllin
CN PTX
CN Torental
CN Trental
FS 3D CONCORD
MF C13 H18 N4 O3
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, SPECINFO, SYNTHLINE, TOXCENTER, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1754 REFERENCES IN FILE CA (1967 TO DATE)
20 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1756 REFERENCES IN FILE CAPLUS (1967 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

REFERENCE 1: 136:156424

REFERENCE 2: 136:145568

REFERENCE 3: 136:144645

REFERENCE 4: 136:139929

REFERENCE 5: 136:130865

REFERENCE 6: 136:130072

REFERENCE 7: 136:128648

REFERENCE 8: 136:123773

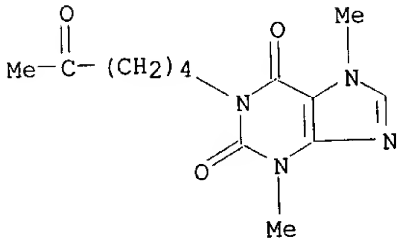
REFERENCE 9: 136:123633

REFERENCE 10: 136:113169

=> d ide can 14

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 222174-99-4 REGISTRY
CN 1H-Purine-2,6-dione, 3,7-dihydro-3,7-dimethyl-1-(5-oxohexyl)-,

monohydrochloride (9CI) (CA INDEX NAME)
MF **C13 H18 N4 O3 . Cl H**
SR CA
LC STN Files: CA, CAPLUS, TOXLIT
CRN (6493-05-6)



● HCl

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 130:272102

=> d ide can 15

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN **140879-24-9** REGISTRY
CN Proteinase, multicatalytic (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 26 S Protease
CN Immunoproteasome
CN Large multicatalytic protease
CN Multicatalytic protease
CN Multicatalytic proteinase
CN Multicatalytic proteinase complex
CN Organelle, proteasome
CN Prosome
CN Proteasome
CN Tricorn protease
CN Tricorn proteinase
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, CA, CAPLUS, CEN, CIN, PROMT, TOXCENTER, TOXLIT, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
2945 REFERENCES IN FILE CA (1967 TO DATE)
23 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2959 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:149805

REFERENCE 2: 136:149021

REFERENCE 3: 136:148714

REFERENCE 4: 136:148435

REFERENCE 5: 136:148432

REFERENCE 6: 136:148424

REFERENCE 7: 136:147905

REFERENCE 8: 136:147058

REFERENCE 9: 136:147011

REFERENCE 10: 136:146815

=> fil medline
FILE 'MEDLINE' ENTERED AT 16:45:20 ON 01 MAR 2002

FILE LAST UPDATED: 28 FEB 2002 (20020228/UP). FILE COVERS 1958 TO DATE.

On April 22, 2001, MEDLINE was reloaded. See HELP RLOAD for details.

MEDLINE now contains IN-PROCESS records. See HELP CONTENT for details.

MEDLINE is now updated 4 times per week. A new current-awareness alert frequency (EVERYUPDATE) is available. See HELP UPDATE for more information.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2001 vocabulary. Enter HELP THESAURUS for details.

The OLDMEDLINE file segment now contains data from 1958 through 1965. Enter HELP CONTENT for details.

Left, right, and simultaneous left and right truncation are available in the Basic Index. See HELP SFIELDS for details.

THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE SUBSTANCE IDENTIFICATION.

=> d all tot

L65 ANSWER 1 OF 10 MEDLINE
AN **2001400588** MEDLINE
DN **21345069** PubMed ID: **11451976**
TI Oral **pentoxifylline** inhibits release of tumor necrosis factor-alpha from human peripheral blood monocytes : a potential treatment for aseptic loosening of total joint components.
AU Pollice P F; Rosier R N; Looney R J; Puzas J E; Schwarz E M; O'Keefe R J
CS Department of Orthopaedics, University of Rochester Medical Center, New York 14642, USA.
NC AR44220 (NIAMS)
AR46545 (NIAMS)
SO JOURNAL OF BONE AND JOINT SURGERY. AMERICAN VOLUME, (2001 Jul) 83-A (7) 1057-61.
Journal code: HJR; 0014030. ISSN: 0021-9355.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200108
ED Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816
AB BACKGROUND: **Pentoxifylline** (Trental) is a methylxanthine-derivative drug that has been used for more than twenty years in the treatment of peripheral vascular disease. **Pentoxifylline** is also a potent inhibitor of tumor necrosis factor-alpha (TNF-alpha) secretion, both in vitro and in vivo, and has demonstrated efficacy in the treatment of certain animal and human inflammatory diseases. **Pentoxifylline**

has a potential therapeutic role in the treatment of aseptic loosening of total joint replacement components because it inhibits TNF-alpha secretion by particle-stimulated human peripheral blood monocytes. The purpose of our study was to determine whether the particle-stimulated secretion of TNF-alpha by peripheral blood monocytes was inhibited in volunteers who had received **pentoxifylline** orally. METHODS: Human peripheral blood monocytes were harvested from eight healthy volunteers and were exposed to three different concentrations of titanium particles or to 500 ng/mL of lipopolysaccharide as a positive control. The same volunteers were then given **pentoxifylline** (400 mg, five times per day) for seven days. Their peripheral blood monocytes were again isolated and exposed to experimental conditions, and the TNF-alpha levels were measured. RESULTS: The peripheral blood monocytes from all eight volunteers showed a significant reduction in TNF-alpha release following oral treatment with **pentoxifylline**. This reduction was observed at exposures of 10(7) and 10(6) titanium particles/mL and in the lipopolysaccharide-treated group, but not at 10(5) particles/mL. CONCLUSIONS: To our knowledge, this is the first study to demonstrate the ability of an oral drug to decrease the release of TNF-alpha from human peripheral blood monocytes exposed ex vivo to particle debris. TNF-alpha is involved in the pathogenesis of osteolysis and subsequent loosening of total joint arthroplasty components. The ability to suppress the release of TNF-alpha in patients with a total joint replacement may help to control osteolysis and to reduce the development of aseptic loosening. This effect could increase implant longevity and decrease the need for revision arthroplasty.

CT Check Tags: Comparative Study; Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Administration, Oral
Adult
Analysis of Variance
Cells, Cultured
Dose-Response Relationship, Drug
Enzyme-Linked Immunosorbent Assay
Equipment Failure Analysis
Joint Prosthesis
Lipopolysaccharides: PD, pharmacology
Monocytes: DE, drug effects
*Monocytes: SE, secretion
***Pentoxifylline: AD, administration & dosage**
Probability
Reference Values
Titanium: PD, pharmacology
*Tumor Necrosis Factor: AN, analysis
*Tumor Necrosis Factor: DE, drug effects
RN **6493-05-6 (Pentoxifylline)**; 7440-32-6 (Titanium)
CN 0 (Lipopolysaccharides); 0 (Tumor Necrosis Factor)

L65 ANSWER 2 OF 10 MEDLINE
AN **2001220237** MEDLINE
DN **21145248** PubMed ID: **11248659**
TI Enhancement of bone morphogenetic protein-2-induced new bone formation in mice by the phosphodiesterase inhibitor **pentoxifylline**.
AU Horiuchi H; Saito N; Kinoshita T; Wakabayashi S; Tsutsumimoto T; Takaoka K
CS Department of Orthopaedic Surgery, Shinshu University School of Medicine, Nagano, Japan.. horiuchi@hsp.md.shinshu-u.ac.jp
SO BONE, (2001 Mar) 28 (3) 290-4.
Journal code: ASR; 8504048. ISSN: 8756-3282.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200105
ED Entered STN: 20010521
Last Updated on STN: 20010521
Entered Medline: 20010517

AB Porous collagen disks (6 mm diameter, 1 mm thickness) were impregnated with recombinant human bone morphogenetic protein-2 (rhBMP-2) (5 microg/disk) and implanted onto the back muscles of mice. **Pentoxifylline** (PTX), which is a methylxanthine-derived inhibitor of phosphodiesterases (PDEs), or vehicle, was injected (5, 25, 50, 100, 200, and 300 mg/kg body weight/day) into the mice subcutaneously once a day for 3 weeks from the day of implantation of the bone morphogenetic protein (BMP)-laden disks. The rhBMP-2-induced ectopic ossicles were harvested and examined using radiographic, histological, and biochemical methods to determine size, bone quality, and calcium content. When compared with controls, ossicles from mice treated with >50 mg/kg per day of PTX were significantly larger in size and had a greater calcium content. However, no differences were noted in mice treated with lower doses (5 and 25 mg/kg per day) of PTX. The temporal sequence of the bone-forming process was unchanged by PTX based on histological examination. The histology of the ossicles from high- and low-dose PTX-treated mice was essentially identical to that observed in the control mice. These experimental results indicate that PTX enhanced the bone-inducing capacity of BMP-2. The underlying mechanism of action most likely involves the inhibition of intracellular phosphodiesterases and a resulting elevation of the intracellular content of cyclic nucleotides. Further studies are warranted to understand how BMP-induced bone formation is pharmacologically modified by PTX.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
***Bone Morphogenetic Proteins: PD, pharmacology**
Bone and Bones: ME, metabolism
Bone and Bones: RA, radiography
Calcium: ME, metabolism
Mice
***Osteogenesis: DE, drug effects**
***Pentoxifylline: PD, pharmacology**
*Phosphodiesterase Inhibitors: PD, pharmacology
Recombinant Proteins: PD, pharmacology

RN **6493-05-6 (Pentoxifylline)**; 7440-70-2 (Calcium)

CN 0 (Bone Morphogenetic Proteins); 0 (Phosphodiesterase Inhibitors); 0 (Recombinant Proteins); 0 (bone morphogenetic protein 2)

L65 ANSWER 3 OF 10 MEDLINE

AN **2001099800** MEDLINE

DN **21029483** PubMed ID: **11192243**

TI Quantitative small-animal surrogate to evaluate drug efficacy in preventing wear debris-induced osteolysis.

AU Schwarz E M; Benz E B; Lu A P; Goater J J; Mollano A V; Rosier R N; Puzas J E; Okeefe R J

CS Department of Medicine, University of Rochester Medical Center, New York 14642, USA.

NC R29 44220 (NIAMS)
RO1 AR45971-01

SO JOURNAL OF ORTHOPAEDIC RESEARCH, (2000 Nov) 18 (6) 849-55.
Journal code: JIQ. ISSN: 0736-0266.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200102

ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010201

AB Individuals who suffer from severe joint destruction caused by the various arthritidies often undergo total joint arthroplasty. A major limitation of this treatment is the development of aseptic loosening of the prosthesis in as many as 20% of patients. The current paradigm to explain aseptic loosening proposes that wear debris generated from the prosthesis initiates a macrophage-mediated inflammatory response by resident macrophages, leading to osteoclast activation and bone resorption at the implant interface. No therapeutic interventions have been proved to

prevent or inhibit aseptic loosening. The development of therapeutic strategies is limited due to the absence of a quantitative surrogate in which drugs can be screened rapidly in large numbers of animals. We have previously described a model in which titanium particles implanted on mouse calvaria induce an inflammatory response with osteolysis similar to that observed in clinical aseptic loosening. Here, we present new methods by which the osteolysis in this model can be quantified. We determined that 6-8-week-old mice in normal health have a sagittal suture area of 50 (+/-6) microm2, which contains approximately five osteoclasts. As a result of the titanium-induced inflammation and osteolysis, the sagittal suture area increases to 197 (+/-27) microm2, with approximately 30 osteoclasts, after 10 days of treatment. The sagittal suture area and the number of osteoclasts in the calvaria of sham-treated mice remained unchanged during the 10 days. We also determined the effects of **pentoxifylline**, a drug that blocks the responses of tumor necrosis factor-alpha to wear debris, and the osteoclast inhibitor alendronate. We found that both drugs effectively block wear debris-induced osteolysis but not osteoclastogenesis. In conclusion, we found the measurements made with this model to be reproducible and to permit quantitative analysis of agents that are to be screened for their potential to prevent aseptic loosening.

CT Check Tags: Animal; Female; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Alendronate: PD, pharmacology
***Arthritis: SU, surgery**
***Arthroplasty: AE, adverse effects**
Cell Division: DE, drug effects
Cell Division: PH, physiology
*Disease Models, Animal
Mice
Mice, Inbred CBA
Osteoclasts: CY, cytology
Osteoclasts: DE, drug effects
Osteoclasts: ME, metabolism
Osteolysis: DT, drug therapy
Osteolysis: ET, etiology
***Osteolysis: PC, prevention & control**
Pentoxifylline: PD, pharmacology
Postoperative Complications: ET, etiology
Postoperative Complications: PP, physiopathology
*Postoperative Complications: PC, prevention & control
***Prostheses and Implants: AE, adverse effects**
Skull: DE, drug effects
Skull: PA, pathology
Skull: PP, physiopathology
Stress, Mechanical
Tumor Necrosis Factor: AI, antagonists & inhibitors
Tumor Necrosis Factor: ME, metabolism
RN **6493-05-6 (Pentoxifylline)**; 66376-36-1 (Alendronate)
CN 0 (Tumor Necrosis Factor)

L65 ANSWER 4 OF 10 MEDLINE
AN **2001086466** MEDLINE
DN **20565394** PubMed ID: **11113392**
TI Phosphodiesterase inhibitors, **pentoxifylline** and rolipram, increase bone mass mainly by promoting bone formation in normal mice.
AU Kinoshita T; Kobayashi S; Ebara S; Yoshimura Y; Horiuchi H; Tsutsumimoto T; Wakabayashi S; Takaoka K
CS Department of Orthopaedic Surgery, Shinshu University School of Medicine, Nagano, Japan.
SO BONE, (2000 Dec) 27 (6) 811-7.
Journal code: ASR. ISSN: 8756-3282.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals

EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118
AB The administration of either **Pentoxifylline** (PTX), a methylxanthine derivative and an inhibitor of cyclic AMP (c-AMP) phosphodiesterases (PDEs), or Rolipram, an inhibitor specific to type-4 PDE (PDE4) in normal mice, significantly increased both cortical and cancellous bone mass. Vertebrae and tibiae from mice treated with PTX or Rolipram were analyzed by means of bone densitometry and histomorphometry. The results revealed that both PTX and Rolipram increased bone mass in normal mice mainly through the acceleration of bone formation. These findings suggest that both PTX and Rolipram can enhance physiological bone formation and thereby increase bone mass in normal mice. The possibility that these agents may be of value for the treatment of osteoporosis is discussed.
CT Check Tags: Animal; Male
***Bone Remodeling: DE, drug effects**
Densitometry, X-Ray
Femur: CY, cytology
Femur: PH, physiology
Femur: RA, radiography
Lumbar Vertebrae: CY, cytology
Lumbar Vertebrae: PH, physiology
Lumbar Vertebrae: RA, radiography
Mice
Mice, Inbred BALB C
Parathyroid Hormones: BL, blood
***Pentoxifylline: PD, pharmacology**
*Phosphodiesterase Inhibitors: PD, pharmacology
*Rolipram: PD, pharmacology
Tibia: CY, cytology
Tibia: PH, physiology
Tibia: RA, radiography
RN 61413-54-5 (Rolipram); **6493-05-6 (Pentoxifylline)**
CN 0 (Parathyroid Hormones); 0 (Phosphodiesterase Inhibitors)

L65 ANSWER 5 OF 10 MEDLINE
AN **2000409211** MEDLINE
DN **20269440** PubMed ID: **10811303**
TI The kinetics of **pentoxifylline** release from drug-loaded hydroxyapatite implants.
AU Slosarczyk A; Szymura-Oleksiak J; Mycek B
CS Faculty of Materials Science and Ceramics, University of Mining and Metallurgy, Cracow, Poland.
SO BIOMATERIALS, (2000 Jun) 21 (12) 1215-21.
Journal code: A4P; 8100316. ISSN: 0142-9612.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200008
ED Entered STN: 20000907
Last Updated on STN: 20000907
Entered Medline: 20000831
AB Hydroxyapatite (HAP) was synthesized by the aqueous precipitation method from CaO and H3 PO4 as the reagents. The HAP powders, either subjected or not subjected to preliminary calcination, were mixed with a pore-creating medium and isostatically shaped at a pressure of 350 MPa to form cylindrical samples. A natural product such as flour served as a pore-creating medium. Sintering was performed in the air, at 1200 or 1250 degrees C. The employed procedure allowed for achieving microporous materials of pore sizes ranging from 0.1 to 15 microm and with open porosity values of 23-44%. It was demonstrated that the porosity of the obtained materials depended mainly on the amount of the added pore-creating medium and the temperature of sintering. The implants,

shaped as hollow cylinders, were filled with 50 mg of **pentoxifylline** (PTX) as a model drug. Internal wells for drug placement were drilled in the samples using a high precision drill. The drug release study was performed in pH = 7.35 phosphate buffer, at 37 degrees C. The results showed that the amount and time of PTX release, as well as the lag time were mainly controlled by the open porosity of the carriers.

CT Check Tags: Support, Non-U.S. Gov't
Biocompatible Materials: CH, chemistry
***Bone Substitutes: CH, chemistry**
Delayed-Action Preparations
Diffusion
Drug Carriers
*Durapatite: CH, chemistry
Flour
Materials Testing
Microscopy, Electron, Scanning
***Pentoxifylline: PK, pharmacokinetics**
Porosity
***Prostheses and Implants**
Solutions

RN 1306-06-5 (Durapatite); **6493-05-6 (Pentoxifylline)**

CN 0 (Biocompatible Materials); 0 (Bone Substitutes); 0 (Delayed-Action Preparations); 0 (Drug Carriers); 0 (Solutions)

L65 ANSWER 6 OF 10 MEDLINE

AN 1998350112 MEDLINE

DN 98350112 PubMed ID: 9683533

TI The ubiquitin-**proteasome** system and cellular proliferation and regulation in osteoblastic cells.

AU Murray E J; Bentley G V; Grisanti M S; Murray S S

CS Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Sepulveda, California, 91343, USA.. murrayes@ucla.edu

NC DK-46804 (NIDDK)

SO EXPERIMENTAL CELL RESEARCH, **(1998 Aug 1)** 242 (2) 460-9. Journal code: EPB; 0373226. ISSN: 0014-4827.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199808

ED Entered STN: 19980903
Last Updated on STN: 20000303
Entered Medline: 19980821

AB The 26S **proteasome** is the macromolecular assembly that mediates ATP- and ubiquitin-dependent extralysosomal intracellular protein degradation in eukaryotes. However, its contribution to the regulation of osteoblast proliferation and hormonal regulation remains poorly defined. Treating osteoblasts with MG-132 or **lactacystin** (membrane-permeable **proteasome** inhibitors) attenuates proliferation. Three **proteasome** activities (peptidylglutamyl-peptide bond hydrolase-, chymotrypsin-, and trypsin-like) were detected in osteoblasts. Catabolic doses of PTH stim-ulated these activities, and cotreatment with PTH and MG-132 blocked stimulation. The **proteasome** alpha- and beta-subunits, polyubiquitins, and large ubiquitin-protein conjugates were detected by Western blotting. A 90-min treatment with 10 nM PTH had no effect on the amount of **proteasome** alpha or beta subunit protein, but increased the relative amount of large ubiquitin-protein conjugates by 200%. MG-132 inhibited deubiquitination of large ubiquitin-protein conjugates. The protein kinase A inhibitor SQ22536 blocked much of the PTH-induced stimulation of MCP activities, while dibutyryl cAMP stimulated it, suggesting that protein kinase A-dependent phosphorylation is important in PTH stimulation of **proteasome** activities. In conclusion, the ubiquitin-**proteasome** system is essential for osteoblast proliferation under control and PTH-treated

conditions. PTH mediates its metabolic effects on the osteoblast, in part, by enhancing ubiquitinylation of protein substrates and stimulating three major **proteasome** activities by a cAMP-dependent mechanism.
Copyright 1998 Academic Press.

CT Check Tags: Animal; Human; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Acetylcysteine: AA, analogs & derivatives
Acetylcysteine: PD, pharmacology
Biopolymers: ME, metabolism
Cell Division: DE, drug effects
Cell Division: PH, physiology
Cell Line
Cyclic AMP: ME, metabolism
Cyclic AMP: PH, physiology
Cyclic AMP-Dependent Protein Kinases: DE, drug effects
Cyclic AMP-Dependent Protein Kinases: ME, metabolism
Cyclic AMP-Dependent Protein Kinases: PH, physiology
Cysteine Endopeptidases: DE, drug effects
*Cysteine Endopeptidases: PH, physiology
Cysteine Proteinase Inhibitors: PD, pharmacology
Leupeptins: PD, pharmacology
Multienzyme Complexes: DE, drug effects
*Multienzyme Complexes: PH, physiology
Osteoblasts: CY, cytology
***Osteoblasts: PH, physiology**
Parathyroid Hormones: PD, pharmacology
Peptide Fragments: PD, pharmacology
Second Messenger Systems: DE, drug effects
Teriparatide: AA, analogs & derivatives
Teriparatide: PD, pharmacology
Tumor Cells, Cultured
Ubiquitin: DE, drug effects
Ubiquitin: ME, metabolism
*Ubiquitin: PH, physiology

RN **133343-34-7 (lactacystin)**; 133407-82-6 (benzyloxycarbonylleucyl-leucyl-leucine aldehyde); 52232-67-4 (Teriparatide); 60-92-4 (Cyclic AMP); 616-91-1 (Acetylcysteine)

CN 0 (Biopolymers); 0 (Cysteine Proteinase Inhibitors); 0 (Leupeptins); 0 (Multienzyme Complexes); 0 (Parathyroid Hormones); 0 (Peptide Fragments); 0 (Ubiquitin); 0 (parathyroid hormone (1-34) amide); EC 2.7.10.- (Cyclic AMP-Dependent Protein Kinases); EC 3.4.22 (Cysteine Endopeptidases); EC 3.4.99.46 (multicatalytic endopeptidase complex)

L65 ANSWER 7 OF 10 MEDLINE
AN **89206249** MEDLINE
DN **89206249** PubMed ID: **2705788**
TI DNA repair and drug resistance: enhancement of the effects of anticancer agents by DNA repair inhibitors.
AU Tomita K; Tsuchiya H; Sasaki T
CS Dept. of Orthopedic Surgery, School of Medicine.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], **(1989 Mar)** 16 (3 Pt 2) 576-84.
Journal code: 6T8; 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS Priority Journals
EM 198905
ED Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890519
AB Recently, it has been revealed that anticancer effects are increased by the inhibition of DNA repair of cancer cells. Methylxanthine is the drug which block DNA repair. In this study we discussed the combined effects of CDDP and caffeine or **pentoxifylline** using human osteosarcoma cells (OST strain). When 2 mM caffeine was added before 1 hr exposure of

CDDP or caffeine and CDDP was added simultaneously for 1 hr, no synergistic effect was shown. On the other hand, marked synergistic growth inhibition was observed when caffeine or **pentoxifylline** was added continuously after 1 hr exposure of CDDP. The addition of caffeine from 24 hr to 48 hr after 1 hr exposure of CDDP also showed synergistic effects as the doubling time of OST cells was about 30 hrs. Further more we treated three patients with advanced osteosarcomas by the combination of CDDP, ADM, and caffeine (p.o.) or that of CDDP and caffeine. A nine-year-old boy with multicentric osteosarcoma treated by the combination of CDDP, ADM, and caffeine showed partial response, and caffeine did not increase the side effects of anticancer agents. Hence the study on overcoming drug resistance by the inhibition of DNA repair will be promising.

CT Check Tags: Human; Male
Adolescence
Antineoplastic Agents, Combined: TU, therapeutic use
Bone Neoplasms: DT, drug therapy
Bone Neoplasms: PA, pathology
*Caffeine: PD, pharmacology
Cell Division
Child
*Cisplatin: PD, pharmacology
*DNA Repair: DE, drug effects
Doxorubicin: AD, administration & dosage
Drug Resistance
Drug Synergism
Middle Age
Osteosarcoma: DT, drug therapy
Osteosarcoma: PA, pathology
Pentoxifylline: PD, pharmacology
Theophylline: PD, pharmacology
Tumor Cells, Cultured: DE, drug effects

RN 15663-27-1 (Cisplatin); 23214-92-8 (Doxorubicin); 58-08-2 (Caffeine); 58-55-9 (Theophylline); **6493-05-6 (Pentoxifylline)**

CN 0 (Antineoplastic Agents, Combined)

L65 ANSWER 8 OF 10 MEDLINE

AN **88223606** MEDLINE

DN **88223606** PubMed ID: **3450443**

TI [Effectiveness of treatment during osteoarticular pain crises in drepanocytosis; based on the example of **pentoxifylline**]. Evaluation de l'efficacite des traitements au cours des crises douloureuses osteo-articulaires de la drepanocytose: exemple de la **pentoxifylline**.

AU Pichard E; Duflo B; Coulibaly S; Mariko B; Monsempes J L; Traore H A; Diallo A D

CS Service de Medecine Interne, Hopital du Point G, Bamako, Mali.

SO BULLETIN DE LA SOCIETE DE PATHOLOGIE EXOTIQUE ET DE SES FILIALES, **(1987)** 80 (5) 834-40.
Journal code: C4G; 7503399. ISSN: 0037-9085.

CY France

DT (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)

LA French

FS Priority Journals

EM 198807

ED Entered STN: 19900308
Last Updated on STN: 19970203
Entered Medline: 19880714

AB Many drugs have been used for prevention and treatment of vaso-occlusive attacks in sickle cell anemia. **Pentoxifylline** is one of the most recent. It increases deformability and filtrability of normal or sickled red cells. In this double-blind study it is compared with a placebo for treatment of 20 osteoarticular crisis during SS or SC sickle cell anemia in Mali. **Pentoxifylline** did not decrease intensity nor duration

of crisis. On the other hand the clinical assessment used for testing drugs efficiency over pain seemed effective and reproducible.

CT Check Tags: Female; Human; Male
Adult
*Anemia, Sickle Cell: PP, physiopathology
Double-Blind Method
Drug Evaluation
Erythrocyte Deformability: DE, drug effects
Hemoglobin SC Disease: BL, blood
*Hemoglobin SC Disease: PP, physiopathology
Joint Diseases: BL, blood
***Joint Diseases: DT, drug therapy**
Joint Diseases: ET, etiology
Pain: BL, blood
*Pain: DT, drug therapy
Pain: ET, etiology
***Pentoxifylline: TU, therapeutic use**
*Theobromine: AA, analogs & derivatives

RN **6493-05-6 (Pentoxifylline)**; 83-67-0 (Theobromine)

L65 ANSWER 9 OF 10 MEDLINE
AN **85133261** MEDLINE
DN **85133261** PubMed ID: **6098626**
TI Study of antiosteoporotic agents in tissue culture.
AU Robin J C; Ambrus J L
SO JOURNAL OF MEDICINE, **(1984)** 15 (4) 319-22.
Journal code: IYG; 7505566. ISSN: 0025-7850.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198504
ED Entered STN: 19900320
Last Updated on STN: 19900320
Entered Medline: 19850419
AB Cultures of osteoblast-like cells were established from calvariae of Sprague-Dawley rats. **Pentoxifylline** increased cAMP levels and calcium uptake in these cultures. However, calcium uptake increased at lower levels than required to increase cAMP levels. Thus, it is likely that cAMP unrelated mechanisms are also involved in these phenomena.
CT Check Tags: Animal
Calcium: ME, metabolism
Cells, Cultured
Cyclic AMP: ME, metabolism
Drug Evaluation, Preclinical
Osteoblasts: ME, metabolism
***Osteoporosis: DT, drug therapy**
***Pentoxifylline: PD, pharmacology**
Pentoxifylline: TU, therapeutic use
Rats
Rats, Inbred Strains
*Theobromine: AA, analogs & derivatives
RN 60-92-4 (Cyclic AMP); **6493-05-6 (Pentoxifylline)**; 7440-70-2 (Calcium); 83-67-0 (Theobromine)

L65 ANSWER 10 OF 10 MEDLINE
AN **83293098** MEDLINE
DN **83293098** PubMed ID: **6310016**
TI Studies on osteoporoses. XI. Effects of a methylxanthine derivative. A preliminary report.
AU Robin J C; Ambrus J L
SO JOURNAL OF MEDICINE, **(1983)** 14 (2) 137-45.
Journal code: IYG; 7505566. ISSN: 0025-7850.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 198310
ED Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19831021
AB Heparin (500 U/kg s.c. B.I.D.) induced significant osteoporosis in C3H/St(Ha) female mice after 3 months of treatment. **Pentoxifylline** (12 mg/kg i.m. B.I.D.) prevented this experimental osteoporosis. Osteoporosis was measured by in vivo neutron activation analysis and results were confirmed by atomic absorption spectroscopy. **Pentoxifylline** (0.1-100 microgram/ml) increased calcium uptake and cAMP production in osteoblast-like bone cells isolated from fetal Sprague-Dawley rats. Theoretical implications for osteoblast control of bone resorption are discussed.
CT Check Tags: Animal; Female
Bone Resorption
Calcium: ME, metabolism
Cyclic AMP: ME, metabolism
Heparin
Mice
Mice, Inbred C3H
Neutron Activation Analysis
Osteoblasts: DE, drug effects
Osteoblasts: ME, metabolism
Osteoporosis: CI, chemically induced
***Osteoporosis: PC, prevention & control**
***Pentoxifylline: TU, therapeutic use**
Rats
Rats, Inbred Strains
Spectrophotometry, Atomic Absorption
Stimulation, Chemical
*Theobromine: AA, analogs & derivatives
RN 60-92-4 (Cyclic AMP); **6493-05-6 (Pentoxifylline)**; 7440-70-2 (Calcium); 83-67-0 (Theobromine); 9005-49-6 (Heparin)

=> fil biosis
FILE 'BIOSIS' ENTERED AT 17:16:50 ON 01 MAR 2002
COPYRIGHT (C) 2002 BIOLOGICAL ABSTRACTS INC.(R)

FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 21 February 2002 (20020221/ED)

=> d all tot

L106 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:161714 BIOSIS
DN PREV200200161714
TI Involvement of phosphodiesterase isozymes in **osteoblastic differentiation.**
AU Wakabayashi, Shinji (1); Tsutsumimoto, Takahiro; Kawasaki, Satoshi; Kinoshita, Tetsuya; Horiuchi, Hiroshi; Takaoka, Kunio
CS (1) Department of Orthopedic Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano Japan
SO Journal of Bone and Mineral Research, (February, 2002) Vol. 17, No. 2, pp. 249-256. print.
ISSN: 0884-0431.
DT Article
LA English
AB The cyclic monophosphate nucleotides (cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP)) are found ubiquitously in mammalian cells and act as second messenger transducers to effect the

intracellular actions of a variety of hormones, cytokines, and neurotransmitters. In turn, these nucleotides also modulate the signal transduction processes regulated by a range of cytokines and growth factors. Previously, we have reported that **pentoxifylline**, a nonselective phosphodiesterase (PDE) inhibitor, can promote **osteoblastic** differentiation by elevating intracellular cAMP levels and, consequently, enhance **bone** formation in vivo and in vitro. In this study, reverse-transcription polymerase chain reaction (RT-PCR) analysis of the **osteoblastic** cell lines, MC3T3-E1 and ST2 revealed the presence of PDE1, PDE2, PDE3, PDE4, PDE7, PDE8, and PDE9. We examined the effect of selective inhibitors for a respective PDE isozyme on the capacity of **bone** morphogenetic protein 4 (BMP-4)-induced alkaline phosphatase (ALP) activity, a cellular differentiation marker, in cells with **osteogenetic** potential. The results indicate that selective inhibitors for PDE2, PDE3, and PDE4 enhanced the BMP-4-induced ALP activity in a dose-dependent manner in ST2 cells but not in MC3T3-E1 cells. Northern blot analysis also revealed that the selective inhibitors for PDE2, PDE3, and PDE4 enhanced the levels of expression of messenger RNAs (mRNAs) of ALP, **osteopontin** (OP), and collagen type I in ST2 cells but not in MC3T3-E1 cells except for the treatment with PDE4 inhibitor. Given these data, we conclude that PDE isozymes are involved in the modulation of **osteoblastic** differentiation mainly at an early stage. Additionally, selective inhibitors for PDE2, PDE3, and PDE4 appear to promote the differentiation of **osteogenic** precursor cells toward an **osteoblastic** phenotype.

CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Enzymes - General and Comparative Studies; Coenzymes *10802
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Developmental Biology - Embryology - General and Descriptive *25502
BC Muridae 86375
IT Major Concepts
Development; Enzymology (Biochemistry and Molecular Biophysics); Skeletal System (Movement and Support)
IT Chemicals & Biochemicals
pentoxifylline: enzyme inhibitor; phosphodiesterase-1; phosphodiesterase-2; phosphodiesterase-3; phosphodiesterase-4; phosphodiesterase-7; phosphodiesterase-8; phosphodiesterase-9
IT Methods & Equipment
reverse transcriptase-polymerase chain reaction: analytical method
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
MC3T3E1 cell line (Muridae): murine **osteoblastic** cells; ST2 cell line (Muridae): murine **osteoblastic** cells
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN **6493-05-6 (PENTOXIFYLLINE)**

L106 ANSWER 2 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:573273 BIOSIS
DN PREV200100573273
TI 1-(5-oxohexyl)-3,7-dimethylxanthine, a phosphodiesterase inhibitor activates MAPK cascades and promotes **osteoblast differentiation** by a mechanism independent of protein kinase A activation.
AU Rawadi, G. (1); Ferrer, C. (1); Spinella-Jaegle, S. (1); Courtois, B. (1); Roman-Roman, S. (1); Bouali, Y. (1); Baron, R. (1)
CS (1) Aventis Pharma, Romainville France
SO Journal of Bone and Mineral Research, (September, 2001) Vol. 16, No. Suppl. 1, pp. S373. print.
Meeting Info.: **Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research** Phoenix, Arizona, USA October 12-16,

2001
ISSN: 0884-0431.
DT **Conference**
LA English
SL English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520**
Cytology and Cytochemistry - General *02502
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Enzymes - General and Comparative Studies; Coenzymes *10802
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Developmental Biology - Embryology - General and Descriptive *25502
BC Muridae 86375
IT Major Concepts
Cell Biology; Development; Skeletal System (Movement and Support)
IT Parts, Structures, & Systems of Organisms
osteoblast: differentiation, skeletal system
IT Chemicals & Biochemicals
1-(5-oxohexyl)-3,7-dimethylxanthine [PeTx, **pentoxifylline**]: phosphodiesterase inhibitor; BMP-2; H89: inhibitor; MAPK [mitogen-activated protein kinase]: cascades; PDE4; PKI; alkaline phosphatase; p38 kinase pathway; phosphodiesterase; phosphodiesterase 1; phosphodiesterase 1-specific inhibitors; phosphodiesterase 2; phosphodiesterase 2-specific inhibitors; phosphodiesterase 3; phosphodiesterase 3-specific inhibitors; phosphodiesterase 4; phosphodiesterase 4-specific inhibitors; phosphodiesterase 5; phosphodiesterase 5-specific inhibitors; protein kinase A: activation
IT Miscellaneous Descriptors
ERK1/2 pathway; **Meeting Abstract**
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
C2C12 cell line (Muridae): rat pluripotent mesenchymal cells; C3H10T1/2 cell line (Muridae): rat pluripotent mesenchymal cells
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN **6493-05-6** (1-(5-OXOHEXYL)-3,7-DIMETHYLXANTHINE)
6493-05-6 (PENTOXIFYLLINE)
142243-02-5 (MITOGEN-ACTIVATED PROTEIN KINASE)
9001-78-9 (ALKALINE PHOSPHATASE)
9025-82-5 (PHOSPHODIESTERASE)
142008-29-5 (PROTEIN KINASE A)

L106 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:525789 BIOSIS
DN PREV200100525789
TI 1-(5-oxohexyl)-3,7-dimethylxanthine, a phosphodiesterase inhibitor, activates MAPK cascades and promotes **osteoblast differentiation** by a mechanism independent of PKA activation (**pentoxyfilline** promotes **osteoblast differentiation**.
AU Rawadi, Georges (1); Ferrer, Caroline; Spinella-Jaegle, Sylviane; Roman-Roman, Sergio; Bouali, Yasmina; Baron, Roland
CS (1) Bone Disease Group, Aventis, 102 route de Noisy, 93230, Romainville Cedex: georges.rawadi@aventis.com France
SO Endocrinology, (November, 2001) Vol. 142, No. 11, pp. 4673-4682. print.
ISSN: 0013-7227.
DT Article
LA English
SL English
AB We have investigated the effect of 1-(5-oxohexyl)-3,7-dimethylxanthine or **pentoxifylline** (PeTx), a nonselective phosphodiesterase inhibitor, on **osteoblastic** differentiation in vitro by using two

mesenchymal cell lines, C3H10T1/2 and C2C12, which are able to acquire the **osteoblastic** phenotype in the presence of **bone** morphogenetic protein-2 (BMP-2). PeTx induced the **osteoblastic** markers, **osteocalcin** and Osf2/Cbfa1, in C3H10T1/2 and C2C12 cells and enhanced BMP-2-induced expression of **osteocalcin**, Osf2/Cbfa1, and alkaline phosphatase. This activity was partially attributed to the fact that PeTx is able to enhance BMP-2-induced Smad1 transcriptional activity. Although PeTx clearly stimulates PKA in these cells, neither pretreatment of cells with the PKA inhibitor H89 nor transfection with the specific PKA inhibitor PKI prevented the induction or enhancement of **osteoblast** markers by PeTx, demonstrating that these effects were independent of PKA activation. On the other hand, PeTx induced the activation of ERK1/2 and p38 kinase pathways independently of the activation of PKA. Selective inhibitors of these MAPK cascades prevented the induction of **osteoblastic** markers in cells treated with PeTx, suggesting that the activation of these two pathways plays a role in the effect of PeTx on **osteoblastic** differentiation.

CC Cytology and Cytochemistry - General *02502
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Enzymes - General and Comparative Studies; Coenzymes *10802
Pathology, General and Miscellaneous - Therapy *12512
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Pharmacology - General *22002

BC Muridae 86375

IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Pharmacology; Skeletal System (Movement and Support)

IT Parts, Structures, & Systems of Organisms
osteoblast: differentiation, skeletal system

IT Chemicals & Biochemicals
1-(5-oxohexyl)-3,7-dimethylxanthine: enzyme inhibitor - drug; ERK1 [extracellular signal-regulated kinase 1]; ERK2 [extracellular signal-regulated kinase 2]; H89: enzyme inhibitor - drug; MAPK [mitogen-activated protein kinase]: activation; Osf2 [Cbfa1]: **osteoblastic** marker; PKA [protein kinase A]: activation; Smad1: transcription; **bone** morphogenetic protein-2 [BMP-2]; **osteocalcin**: **osteoblastic** marker; p38 kinase; **pentoxifylline**: enzyme inhibitor - drug; phosphodiesterase

ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
C2C12 cell line (Muridae): murine pluripotent mesenchymal cells; C3H10T1 cell line (Muridae): murine pluripotent mesenchymal cells; C3H10T2 cell line (Muridae): murine pluripotent mesenchymal cells

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates

RN **6493-05-6** (1-(5-OXOHEXYL)-3,7-DIMETHYLXANTHINE)
137632-07-6 (EXTRACELLULAR SIGNAL-REGULATED KINASE 1)
137632-08-7 (EXTRACELLULAR SIGNAL-REGULATED KINASE 2)
142243-02-5 (MITOGEN-ACTIVATED PROTEIN KINASE)
142008-29-5 (PROTEIN KINASE A)
70563-21-2 (SMAD1)
165245-96-5 (P38 KINASE)
6493-05-6 (PENTOXIFYLLINE)
9025-82-5 (PHOSPHODIESTERASE)

L106 ANSWER 4 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:216180 BIOSIS
DN PREV200100216180
TI Enhancement of **bone morphogenetic protein** -2-induced new **bone** formation in mice by the phosphodiesterase inhibitor **pentoxifylline**.

AU Horiuchi, H. (1); Saito, N.; Kinoshita, T.; Wakabayashi, S.; Tsutsumimoto, T.; Takaoka, K.
CS (1) Department of Orthopaedic Surgery, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano: horiuchi@hsp.md.shinshu-u.ac.jp Japan
SO Bone (New York), (March, 2001) Vol. 28, No. 3, pp. 290-294. print. ISSN: 8756-3282.
DT Article
LA English
SL English
AB Porous collagen disks (6 mm diameter, 1 mm thickness) were impregnated with recombinant human **bone** morphogenetic protein-2 (rhBMP-2) (5 mug/disk) and implanted onto the back muscles of mice. **Pentoxifylline** (PTX), which is a methylxanthine-derived inhibitor of phosphodiesterases (PDEs), or vehicle, was injected (5, 25, 50, 100, 200, and 300 mg/kg body weight/day) into the mice subcutaneously once a day for 3 weeks from the day of implantation of the **bone** morphogenetic protein (BMP)-laden disks. The rhBMP-2-induced ectopic ossicles were harvested and examined using radiographic, histological, and biochemical methods to determine size, **bone** quality, and calcium content. When compared with controls, ossicles from mice treated with >50 mg/kg per day of PTX were significantly larger in size and had a greater calcium content. However, no differences were noted in mice treated with lower doses (5 and 25 mg/kg per day) of PTX. The temporal sequence of the **bone**-forming process was unchanged by PTX based on histological examination. The histology of the ossicles from high- and low-dose PTX-treated mice was essentially identical to that observed in the control mice. These experimental results indicate that PTX enhanced the **bone**-inducing capacity of BMP-2. The underlying mechanism of action most likely involves the inhibition of intracellular phosphodiesterases and a resulting elevation of the intracellular content of cyclic nucleotides. Further studies are warranted to understand how BMP-induced **bone** formation is pharmacologically modified by PTX.
CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Pathology, General and Miscellaneous - Therapy *12512
Muscle - Physiology and Biochemistry *17504
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Endocrine System *22016
BC Hominidae 86215
Muridae 86375
IT Major Concepts
Skeletal System (Movement and Support); Pharmacology
IT Parts, Structures, & Systems of Organisms
bone: formation, skeletal system; muscle: muscular system
IT Chemicals & Biochemicals
bone morphogenetic protein-2; collagen;
pentoxifylline: hormone - drug, phosphodiesterase inhibitor
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); mouse (Muridae)
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Primates; Rodents; Vertebrates
RN **6493-05-6 (PENTOXIFYLLINE)**

L106 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:444706 BIOSIS
DN PREV199900444706
TI **Pentoxifylline** enhances BMP-4-induced **differentiation** of immature **osteoblasts lineages**.

AU Tsutsumimoto, Takahiro (1); Wakabayashi, Shinji (1); Kinoshita, Tetsuya (1); Horiuchi, Hiroshi (1); Takaoka, Kunio (1)
CS (1) Department of Orthopaedic Surgery, Shinshu University School of Medicine, Matsumoto, Nagano Japan
SO Journal of Bone and Mineral Research, (Sept., 1999) Vol. 14, No. SUPPL. 1, pp. S354.
Meeting Info.: **Twenty-First Annual Meeting of the American Society for Bone and Mineral Research** St. Louis, Missouri, USA September 30-October 4, 1999 American Society for Bone and Mineral Research
. ISSN: 0884-0431.
DT **Conference**
LA English
CC **Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004**
Cytology and Cytochemistry - Animal *02506
Bones, Joints, Fasciae, Connective and Adipose Tissue - Pathology *18006
Pharmacology - Connective Tissue, Bone and Collagen - Acting Drugs *22012
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
BC Mammalia - Unspecified 85700
Muridae 86375
IT Major Concepts
Cell Biology; Pharmacology; Skeletal System (Movement and Support)
IT Diseases
osteoporosis: **bone** disease
IT Chemicals & Biochemicals
cyclic AMP; **pentoxifylline**: enzyme inhibitor - drug; BMP-4
IT Alternate Indexing
Osteoporosis (MeSH)
IT Miscellaneous Descriptors
cell differentiation; **Meeting Abstract**
ORGN Super Taxa
Mammalia: Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
MC3T3-E1 cell line (Muridae); ST2 cell line (Mammalia); 10T1/2 cell line (Mammalia)
ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Rodents; Vertebrates
RN **6493-05-6 (PENTOXIFYLLINE)**
60-92-4 (CYCLIC AMP)

L106 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:125999 BIOSIS
DN PREV199800125999
TI An overview of the methylxanthines and their regulation in the horse.
AU Harkins, J. Daniel (1); Rees, W. Allan (1); **Mundy, George D.**; Stanley, Scott D.; Tobin, Thomas
CS (1) Maxwell H. Gluck Equine, Res. Cent., Dep. Vet. Sci., Univ. Kentucky, Lexington, KY 40506 USA
SO Equine Practice, (Jan., 1998) Vol. 20, No. 1, pp. 10-16.
ISSN: 0162-8941.
DT Article
LA English
AB Caffeine, theophylline and theobromine are naturally occurring members of the methylxanthine family, **pentoxifylline**, dyphylline and enprofylline are structurally related synthetic pharmaceuticals. Caffeine has predominantly central nervous system effects, theophylline, dyphylline and enprofylline have predominantly bronchodilator effects, while theobromine is associated with diuretic responses. **Pentoxifylline** is thought to increase red cell deformability and facilitate blood flow through capillary beds. The methylxanthines are not highly potent agents;

they are typically administered in gram doses and they tend to have relatively long plasma half-lives. They remain detectable in plasma and urine for relatively long periods. Similarly, traces of the naturally occurring members of this family are not uncommonly identified in forensic samples. In this **review** we report on the detection, actions, uses and regulatory control of this group of agents in performance horses.

CC Pharmacology - General *22002
General Biology - Forensic Science *00531
Metabolism - General Metabolism; Metabolic Pathways *13002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Veterinary Science - General; Methods *38002
Blood, Blood-Forming Organs and Body Fluids - General; Methods *15001
Urinary System and External Secretions - General; Methods *15501

BC Equidae 86145

IT Major Concepts
Forensics; Pharmacology; Veterinary Medicine (Medical Sciences)

IT Chemicals & Biochemicals
caffeine: analytical detection, clinical dose, half-life, metabolism, plasma threshold, urine threshold, pharmacokinetics; dyphylline: analytical detection, clinical dose, half-life, plasma threshold, urine threshold, pharmacokinetics, metabolism; enprofylline: analytical detection, urine threshold, plasma threshold, pharmacokinetics, clinical dose, metabolism, half-life; methylxanthines: analytical detection, half-life, pharmacokinetics, urine threshold, plasma threshold, metabolism, clinical dose; **pentoxifylline**: analytical detection, urine threshold, clinical dose, metabolism, plasma threshold, pharmacokinetics, half-life; theobromine: analytical detection, urine threshold, plasma threshold, pharmacokinetics, metabolism, half-life, clinical dose; theophylline: analytical detection, urine threshold, plasma threshold, metabolism, pharmacokinetics, half-life, clinical dose

IT Miscellaneous Descriptors
drug regulations; horse racing; racehorse testing; running performance

ORGN Super Taxa
Equidae: Perissodactyla, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
horse (Equidae)

ORGN Organism Superterms
Animals; Chordates; Mammals; Nonhuman Mammals; Nonhuman Vertebrates; Perissodactyls; Vertebrates

RN 28109-92-4D (METHYLXANTHINES)
58-08-2 (CAFFEINE)
58-55-9 (THEOPHYLLINE)
83-67-0 (THEOBROMINE)
479-18-5 (DYPHYLLINE)
41078-02-8 (ENPROFYLLINE)
6493-05-6 (PENTOXIFYLLINE)

L106 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:300447 BIOSIS
DN PREV199799599650
TI The trental influence on collagen proteolysis in experimental aseptic infarction of the **long bone**.
AU Magomedov, S.; Grigorovskii, V. V.
CS Ukr. Res. Inst. Traumatol. Orthop., Ukr. Minist. Health, Kiev Ukraine
SO Ukrainskii Biokhimicheskii Zhurnal, (1996) Vol. 68, No. 5, pp. 69-76. ISSN: 0201-8470.
DT Article
LA Russian
SL Ukrainian; English
AB Dynamics of biochemical parameters of the connective tissue and morphometric parameters of lesion were studied in rabbits with induced embolic aseptic infraction of the femur without and with the trental (**pentoxyphyllin**) treatment. The correlation was found between the pairs of indices: proteolytic activity and **bone** marrow necrosis volume: collagenase activity and **bone** cortex remodelling rate:

concentration of protein bound with hydroxyprolin fraction and endosteal regenerate volume.
CC Biochemical Studies - General *10060
Cardiovascular System - General; Methods *14501
Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods *18001
Pharmacology - General *22002
BC Leporidae *86040
IT Major Concepts
Biochemistry and Molecular Biophysics; Cardiovascular System (Transport and Circulation); Pharmacology; Skeletal System (Movement and Support)
IT Chemicals & Biochemicals
TRENTAL; **PENTOXIFYLLINE**; COLLAGENASE
IT Miscellaneous Descriptors
ASEPTIC INFARCTION; **BONE** CORTEX REMODELLING RATE; **BONE** DISEASE; **BONE** MARROW NECROSIS VOLUME; COLLAGEN PROTEOLYSIS; COLLAGENASE ACTIVITY; ENDOSTEAL REGENERATE VOLUME; EXPERIMENTAL; FEMUR; LONG **BONE**; **PENTOXIFYLLINE**; **PENTOXYPHYLLIN**; PHARMACOLOGY; SKELETAL SYSTEM; TRENTAL INFLUENCE; VASCULAR DISEASE; VASODILATOR-DRUG
ORGN Super Taxa
Leporidae: Lagomorpha, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
rabbit (Leporidae)
ORGN Organism Superterms
animals; chordates; lagomorphs; mammals; nonhuman mammals; nonhuman vertebrates; vertebrates
RN **6493-05-6** (TRENTAL)
6493-05-6 (PENTOXIFYLLINE)
9001-12-1 (COLLAGENASE)

L106 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1985:93919 BIOSIS
DN BR28:93919
TI STUDY OF **ANTIOSTEOPOROTIC** AGENTS IN TISSUE CULTURE.
AU ROBIN J C; AMBRUS J L
CS ROSWELL PARK MEMORIAL INST., BUFFALO, NY 14263.
SO J. Med. (Westbury, N. Y.), (1984 (RECD 1985)) 15 (4), 319-322.
CODEN: JNMDBO. ISSN: 0025-7850.
FS BR; OLD
LA English
CC Biochemical Studies - General 10060
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Bones, Joints, Fasciae, Connective and Adipose Tissue - General; Methods *18001
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Connective Tissue, Bone and Collagen - Acting Drugs *22012
Tissue Culture, Apparatus, Methods and Media 32500
BC Muridae 86375
IT Miscellaneous Descriptors
RAT **PENTOXIFYLLINE** METABOLIC-DRUG CYCLIC AMP
RN 60-92-4 (CYCLIC AMP)
6493-05-6 (PENTOXIFYLLINE)

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 17:31:08 ON 01 MAR 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 1 Mar 2002 VOL 136 ISS 10
FILE LAST UPDATED: 28 Feb 2002 (20020228/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the CAS files between 12/27/01 and 1/23/02. As of 1/23/02, the situation has been resolved. Searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator executed between 12/27/01 and 1/23/02 may be incomplete. See the NEWS message on this topic for more information.

=> d all tot

L140 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 2001:300537 HCAPLUS
DN 134:331618
TI Inhibitors of proteasomal activity for stimulating **bone** and hair growth
IN **Mundy, Gregory R.; Garrett, Ross I.; Rossini, G.**
PA **Osteoscreen, Inc., USA**
SO PCT Int. Appl., 57 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K038-06
ICS A61K038-07; A61K038-13; A61K031-165; A61K031-365; A61K031-4015; A61K031-522; A61P019-00; A61P043-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 62
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001028579	A2	20010426	WO 2000-US41360	20001020
	WO 2001028579	A3	20010920		

W: AU, CA, JP
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI	US 1999-421545	A	19991020
	US 2000-558973	A	20000425

AB Compds. that inhibit the activity of NF-.kappa.B or inhibit the activity of the proteasome or both promote **bone** formation and hair growth and are thus useful in treating **osteoporosis, bone** fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic **bone** disease, **osteolytic bone** disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation; they also stimulate the prodn. of hair follicles and are thus useful in stimulating hair growth, including hair d., in subject where this is desirable. N-carbobenzyol-Ile-Glu-(OtBu)Ala-Leu-CHO (PSI) in 50% propylene glycol, 10% DMSO, and 40% water was injected daily for 5 days (1mg/kg body

wt./day) into the s.c. tissue of mice and the tissue was examd. histol. 16 days later. The no. of hair follicles increased and the downward extension of these hair follicles into the dermal tissue was noted, which are hallmarks of anagen. There was an obvious increase in size of the follicle diam. and the root sheath diam.

ST proteasome inhibitor hair **bone** growth stimulant

IT Transcription factors
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(I.kappa.B (inhibitor of NF-.kappa.B); inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT Periodontium
Tooth
(disease; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT Hair
(follicle; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT **Bone**, disease
(fracture; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT **Bone**
Hair preparations
(growth stimulants; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT Dental materials and appliances
(implants; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT **Bone** formation
(inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT **Bone** morphogenetic proteins
Estrogens
Growth factors, animal
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT **Bone**, disease
(metastatic and **osteolytic**; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT Growth factors, animal
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**osteogenins**; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT Surgery
(post-plastic; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT Hyperparathyroidism
(secondary; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT Phosphoproteins
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(statins; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT Joint, anatomical
(surgery of; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT **Osteoporosis**
(therapeutic agents; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT 13598-36-2D, Phosphonic acid, alkylidenebis- derivs.
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(bisphosphonate; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT 67-99-2, Gliotoxin 404-86-4, Capsaicin **6493-05-6**, PTX 9035-81-8, Trypsin inhibitor 25769-03-3, PDTC 59865-13-3, Cyclosporin a 65240-86-0, PPM 18 79902-63-9, Simvastatin 110044-82-1 110115-07-6 **133343-34-7**, **Lactacystin** 133407-82-6, MG 132 133407-86-0, MG 115 **134381-21-8**, **Epoxomicin** 158442-41-2D, PSI, epoxides 179324-22-2, MG 262 179324-69-7, PS 341 336099-20-8 336099-21-9 336608-38-9, Bay 11-7082
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors of proteasomal activity for stimulating **bone** and hair growth)

IT 140879-24-9, Proteasome
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; inhibitors of proteasomal activity for stimulating **bone** and hair growth)

L140 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 2000:53374 HCAPLUS
DN 132:102860
TI Inhibitors of **proteasomal** activity for stimulating **bone** and hair growth
IN **Mundy, Gregory R.; Garrett, I. Ross; Rossini, G.**
PA **Osteoscreen, USA**
SO PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DT Patent
LA English
IC ICM A61K031-00
CC 1-12 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000002548	A2	20000120	WO 1999-US15533	19990709 <--
W: AL, AM, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HU, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SD, SG, SI, SK, TR, TT, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9963109	A1	20000201	AU 1999-63109	19990709 <--
EP 1096924	A1	20010509	EP 1999-933827	19990709 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI US 1998-113947	A1	19980710 <--		
WO 1999-US15533	W	19990709		

AB Compds. that inhibit the activity of NF-.kappa.B or inhibit the activity of the **proteasome** or both promote **bone** formation and hair growth and are thus useful in treating **osteoporosis**, **bone** fracture or deficiency, primary or secondary **hyperparathyroidism**, **periodontal** disease or defect, metastatic **bone** disease, **osteolytic bone** disease, post-plastic surgery, post-prosthetic joint surgery, and post-**dental** implantation. They also stimulate the prodn. of hair follicles and are thus useful in stimulating hair growth, including hair d., in subject where this is desirable.

ST hair **bone** growth stimulation NFkappaB inhibitor; **proteasome** inhibitor hair **bone** growth stimulation

IT Transcription factors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(NF-.kappa.B (nuclear factor .kappa.B); NF-.kappa.B inhibitors and

inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Bone formation**
Drug delivery systems
Drug screening
(NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Bone** morphogenetic proteins
Estrogens
Growth factors, animal
Hormones, animal, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth, and use with other agents)

IT Antitumor agents
(**bone**, metastasis; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Skull**
(calvarium, calvarial **bone** growth assay; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Cartilage**
(cartilage-derived morphogenetic proteins; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth, and use with other agents)

IT Joint, anatomical
(degeneration; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Disease, animal
(**dental**; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Periodontium**
(disease; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Hair
(follicle; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Bone, disease**
(fracture, and **bone** deficiency; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Bone**
(growth promoters; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth, and use with other agents)

IT Hair preparations
(growth stimulants; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Dental materials and appliances**
(**implants**, post-**dental** implantation; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Cell differentiation
(inducers; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth, and use with other agents)

IT **Bone, neoplasm**
(**metastasis**, inhibitors; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(morphogenetic, cartilage-derived; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth, and use with other agents)

IT Growth factors, animal
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**osteogenins**; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth, and use with other agents)

IT **Bone, disease**
(**osteolytic**; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Isoprenoids
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pathway; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(peptidic aldehydes; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Aldehydes**, biological studies
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**peptidyl**; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Surgery
(plastic, post-plastic surgery; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Joint, anatomical
Prosthetic materials and Prosthetics
(post-prosthetic joint surgery; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Hyperparathyroidism**
(primary; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Proteins, specific or class
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**proteasome**; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Bone**
(resorption, inhibitors; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth, and use with other agents)

IT **Hyperparathyroidism**
(secondary; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT **Osteoporosis**
(therapeutic agents; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT Drug delivery systems
(topical; NF-.kappa.B inhibitors and inhibitors of **proteasomal** activity for stimulating **bone** and hair growth)

IT 67-99-2, Gliotoxin 404-86-4, Capsaicin **6493-05-6, Pentoxifylline** 59865-13-3, Cyclosporin A 79902-63-9,

Simvastatin 106096-93-9, Basic fibroblast growth factor 110044-82-1
110115-07-6 **133343-34-7**, **Lactacystin** 133407-82-6, MG
132 133407-86-0, MG 115 158442-41-2 179324-22-2, MG 262
RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(NF-.kappa.B inhibitors and inhibitors of **proteasomal**
activity for stimulating **bone** and hair growth)

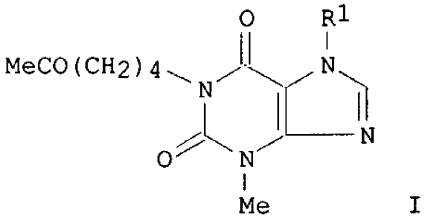
IT **140879-24-9**, **Proteasome**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL
(Biological study); PROC (Process)
(NF-.kappa.B inhibitors and inhibitors of **proteasomal**
activity for stimulating **bone** and hair growth)

IT 13598-36-2D, Phosphonic acid, bisphosphonates
RL: BAC (Biological activity or effector, except adverse); THU
(Therapeutic use); BIOL (Biological study); USES (Uses)
(and statins; NF-.kappa.B inhibitors and inhibitors of
proteasomal activity for stimulating **bone** and hair
growth, and use with other agents)

L140 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:228011 HCAPLUS
DN 130:306602
TI Xanthine derivatives for prevention and treatment of **bone**
diseases
IN Takaoka, Kunio
PA Hoechst Marion Roussel K. K., Japan
SO Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K031-52
ICS A61K031-52; C07D473-06
CC 1-10 (Pharmacology)
FAN.CNT 1

	PATENT NO.	KIND	DATE		APPLICATION NO.	DATE
PI	JP 11092379	A2	19990406		JP 1998-216566	19980716 <--
PRAI	JP 1997-212713		19970724	<--		

GI



I

AB Xanthine derivs. (I; R1 = C1-3 straight- or branched-chain alkyl) and
their salts, including 1-(5-oxohexyl)-3,7-dimethylxanthine and
1-(5-oxohexyl)-3-methyl-7-propylxanthine, are claimed for prevention and
treatment of **bone** diseases, including **osteoporosis**.
The effects of I on TNF-.alpha.-induced **bone** resorption and
bone healing after fracture were tested.

ST xanthine deriv **bone** disease TNF alpha; **antiosteoporotic**
xanthine deriv

IT **Antiosteoporotic** agents
Bone diseases
Bone fracture
Bone resorption

(xanthine derivs. for prevention and treatment of **bone** diseases)

IT Tumor necrosis factor .alpha.
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(xanthine derivs. for prevention and treatment of **bone** diseases)

IT 69-89-6D, Xanthine, derivs. **6493-05-6**, 1-(5-Oxohexyl)-3,7-dimethylxanthine 55242-55-2, 1-(5-Oxohexyl)-3-methyl-7-propylxanthine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(xanthine derivs. for prevention and treatment of **bone** diseases)

L140 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:557820 HCAPLUS
DN 129:255313
TI **Proparathyroid** hormone-related protein is associated with the chaperone protein BiP and undergoes **proteasome**-mediated degradation
AU Meerovitch, Karen; Wing, Simon; Goltzman, David
CS Calcium Research Laboratory, Department of Medicine, McGill University, Montreal, PQ, H3A 1A1, Can.
SO J. Biol. Chem. (**1998**), 273(33), 21025-21030
CODEN: JBCHA3; ISSN: 0021-9258
PB American Society for Biochemistry and Molecular Biology
DT Journal
LA English
CC 2-7 (Mammalian Hormones)
AB **Parathyroid** hormone-related peptide (PTHrP) is an important causal factor for hypercalcemia assocd. with malignancy. In addn. to the endocrine functions attributed to secretory forms of the peptide, PTHrP also plays a local role as a mediator of cellular growth and differentiation presumably at least in part through intracellular pathways. In studying the post-translational regulation of PTHrP, the authors obsd. that PTHrP was conjugated to multiple ubiquitin moieties. The authors report that the **proteasome** is responsible for the degrdn. of the endoplasmic reticulum-assocd. precursor, pro-PTHrP. Cells expressing prepro-PTHrP and exposed to **lactacystin** accumulate pro-PTHrP assessed by anti-pro specific antibodies. Brefeldin A-treated cells also accumulate pro-PTHrP suggesting that degrdn. does not occur in the endoplasmic reticulum (ER) lumen. Subcellular fractionation of both **lactacystin** and brefeldin A-treated cells indicated that accumulated pro-PTHrP resides in microsomal fractions with a portion of the protein exposed to the cytosolic side of the ER membrane as assessed by protease protection expts. Immunopptn. and Western blot anal. identified pro-PTHrP in assocn. with the ER mol. chaperone protein BiP. The authors conclude that pro-PTHrP from the ER can gain access to the cytoplasmic side of the ER membrane where it can undergo ubiquitination and degrdn. by the **proteasome**.
ST proPTHrP degrdn **proteasome** BiP endoplasmic reticulum
IT Cytoplasm
Endoplasmic reticulum
Intracellular transport
Microsome
(**proparathyroid** hormone-related protein is assocd. with the chaperone protein BiP and undergoes **proteasome**-mediated degrdn.)
IT GRP78 (protein)
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**proparathyroid** hormone-related protein is assocd. with the chaperone protein BiP and undergoes **proteasome**-mediated degrdn.)
IT 103370-86-1, **Parathyroid** hormone-related peptide
RL: BOC (Biological occurrence); BPR (Biological process); BIOL

(Biological study); OCCU (Occurrence); PROC (Process)
(pro-; **proparathyroid** hormone-related protein is assocd. with the chaperone protein BiP and undergoes **proteasome**-mediated degrdn.)

IT **140879-24-9, Proteasome**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**proparathyroid** hormone-related protein is assocd. with the chaperone protein BiP and undergoes **proteasome**-mediated degrdn.)

IT 60267-61-0, Ubiquitin
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(**proparathyroid** hormone-related protein is assocd. with the chaperone protein BiP and undergoes **proteasome**-mediated degrdn.)

L140 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:515597 HCAPLUS
DN 129:214801
TI The ubiquitin-**proteasome** system and cellular proliferation and regulation in **osteoblastic** cells
AU Murray, Elsa J. Brochmann; Bentley, Gregory V.; Grisanti, Mario S.; Murray, Samuel S.
CS Geriatric Research, Education and Clinical Center, Department of Veterans Affairs Medical Center, Sepulveda, CA, 91343, USA
SO Exp. Cell Res. (**1998**), 242(2), 460-469
CODEN: ECREAL; ISSN: 0014-4827
PB Academic Press
DT Journal
LA English
CC 13-6 (Mammalian Biochemistry)
Section cross-reference(s): 2
AB The 26S **proteasome** is the macromol. assembly that mediates ATP- and ubiquitin-dependent extralysosomal intracellular protein degrdn. in eukaryotes. However, its contribution to the regulation of **osteoblast** proliferation and hormonal regulation remains poorly defined. Treating **osteoblasts** with MG-132 or **lactacystin** (membrane-permeable **proteasome** inhibitors) attenuates proliferation. Three **proteasome** activities (peptidylglutamylpeptide bond hydrolase-, chymotrypsin-, and trypsin-like) were detected in **osteoblasts**. Catabolic doses of PTH stimulated these activities, and cotreatment with PTH and MG-132 blocked stimulation. The **proteasome** .alpha.- and .beta.-subunits, polyubiquitins, and large ubiquitin-protein conjugates were detected by Western blotting. A 90-min treatment with 10 nM PTH had no effect on the amt. of **proteasome** .alpha. or .beta. subunit protein, but increased the relative amt. of large ubiquitin-protein conjugates by 200%. MG-132 inhibited deubiquitination of large ubiquitin-protein conjugates. The protein kinase A inhibitor SQ22536 blocked much of the PTH-induced stimulation of MCP activities, while dibutyryl cAMP stimulated it, suggesting that protein kinase A-dependent phosphorylation is important in PTH stimulation of **proteasome** activities. In conclusion, the ubiquitin-**proteasome** system is essential for **osteoblast** proliferation under control and PTH-treated conditions. PTH mediates its metabolic effects on the **osteoblast**, in part, by enhancing ubiquitinylation of protein substrates and stimulating three major **proteasome** activities by a cAMP-dependent mechanism. (c) 1998 Academic Press.
ST **parathyroid** hormone ubiquitin **proteasome** **osteoblast** proliferation; protein kinase A **proteasome** **osteoblast** proliferation
IT Protein phosphorylation
(PTH mediates its metabolic effects on **osteoblast** by enhancing ubiquitinylation of protein substrates and stimulating three major **proteasome** activities by cAMP-dependent mechanism)

IT Proteins (specific proteins and subclasses)
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(conjugates with ubiquitin; PTH mediates its metabolic effects on **osteoblast** by enhancing ubiquitinylation of protein substrates and stimulating three major **proteasome** activities by cAMP-dependent mechanism)

IT Cell proliferation
Osteoblast
(ubiquitin-**proteasome** system and cellular proliferation and regulation in **osteoblastic** cells)

IT **140879-24-9, Proteasome**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(26S; ubiquitin-**proteasome** system and cellular proliferation and regulation in **osteoblastic** cells)

IT 60-92-4, CAMP 9002-07-7, Trypsin 9002-64-6, **Parathyroid** hormone 9004-07-3, Chymotrypsin 142008-29-5, Protein kinase A 144697-23-4, Peptidylglutamylpeptide hydrolase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(PTH mediates its metabolic effects on **osteoblast** by enhancing ubiquitinylation of protein substrates and stimulating three major **proteasome** activities by cAMP-dependent mechanism)

IT 60267-61-0D, Ubiquitin, conjugates with proteins
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(PTH mediates its metabolic effects on **osteoblast** by enhancing ubiquitinylation of protein substrates and stimulating three major **proteasome** activities by cAMP-dependent mechanism)

IT 120904-94-1, Polyubiquitin
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(ubiquitin-**proteasome** system and cellular proliferation and regulation in **osteoblastic** cells)

L140 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1998:347321 HCAPLUS
DN 129:104675
TI Inflammation-associated lysyl oxidase protein expression in vivo, and modulation by FGF-2 plus IGF-1
AU Trackman, P. C.; Graham, Rudolph J.; Bittner, Howard K.; Carnes, David L.; Gilles, James A.; Graves, Dana T.
CS Division of Oral Biology, Boston University Medical Center, 700 Albany Street, W-201E, Boston, MA, 02118, USA
SO Histochem. Cell Biol. (**1998**), 110(1), 9-14
CODEN: HCBIFP; ISSN: 0948-6143
PB Springer-Verlag
DT Journal
LA English
CC 2-10 (Mammalian Hormones)
Section cross-reference(s): 14
AB Lysyl oxidase is the extracellular enzyme that catalyzes oxidative deamination of **peptidyl**-lysine residues in elastin precursors, and lysine and hydroxylysine residues in collagen precursors to form **peptidyl-aldehydes**. These **aldehydes** then spontaneously condense to crosslink collagen and elastin and thereby allow the formation of a mature and functional extracellular matrix. In the present study, cryosections made from aseptic immune-induced periapical lesions exptl. generated in lab. rats were examd. by immunohistochem. to investigate whether lysyl oxidase protein expression is altered in inflamed oral tissues. Periapical lesions are exptl. induced endodontic lesions of **tooth** roots. In addn., the effect of administration of a mixt. of fibroblast growth factor (FGF)-2 and insulin-like growth factor (IGF)-1 into these lesions on lysyl oxidase expression was detd. Lysyl oxidase expression was found to be increased in nonmineralized

connective tissue adjacent to inflamed lesions. Morphometric analyses indicated that max. lysyl oxidase expression occurred at a discrete distance from the lesion not exceeding 350 .mu.m from the inflammatory cells. Staining was assocd. with mesenchymal cells with a fibroblastic morphol. No lysyl oxidase staining was found near **teeth** where no lesion was induced. Application of a mixt. of FGF-2 and IGF-1 resulted in a further twofold increase in lysyl oxidase expression. These results provide a new in vivo model to study lysyl oxidase regulation, and suggest that inflammatory cells may control lysyl oxidase expression in oral tissues, possibly by a mechanism involving secretion of cytokines and other factors, probably contributing to the regulation of extracellular matrix accumulation.

ST inflammation lysyl oxidase FGF2 IGF

IT **Connective tissue**
Dental caries
Fibroblast
Inflammation
(inflammation-assocd. lysyl oxidase expression modulation by FGF-2 plus IGF-I)

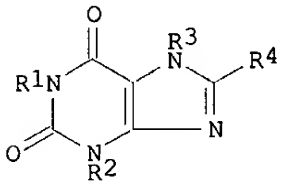
IT 67763-96-6, IGF-1 106096-93-9, Fibroblast growth factor 2
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(inflammation-assocd. lysyl oxidase expression modulation by FGF-2 plus IGF-I)

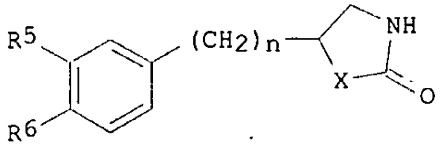
IT 9059-25-0, Lysyl oxidase
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(inflammation-assocd. lysyl oxidase expression modulation by FGF-2 plus IGF-I)

L140 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:556008 HCAPLUS
DN 127:156735
TI Phosphodiesterase IV inhibitors for treatment of **osteoporosis**
IN Miyamoto, Kenichi; Kasugai, Shohei; Waki, Takahiro; Sawanishi, Hiroyuki
PA Miyamoto, Kenichi, Japan
SO Jpn. Kokai Tokkyo Koho, 9 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K045-00
ICS A61K031-40; A61K031-415; A61K031-52; C07D207-26; C07D233-34; C07D473-06; C12N009-99
CC 1-10 (Pharmacology)
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 09169665	A2	19970630	JP 1995-354850	19951221 <--

OS MARPAT 127:156735
GI


I


II

AB Phosphodiesterase IV inhibitors I (R1 = H, low alkyloxyl, C1-C6 alkyl with or without acyl substitution; R2 = H, low alkyl; R3 = H, low alkyl with or without acyl substitution; R4 = H, C3-C7 cycloalkyl) e.g. xanthine derivs. or II (R5, R6 = low alkyloxyl, C3-C7 cycloalkyloxyl; n = 0 or 1; X =

-CH2- or -NH-) and their pharmaceutical acceptable salts are claimed for treatment of **osteoporosis**. The phosphodiesterase IV-inhibiting and **bone** formation-stimulating actions of I and II were tested.

ST phosphodiesterase IV inhibitor xanthine deriv **osteoporosis**

IT **Antiosteoporotic** agents
Bone formation
(phosphodiesterase IV inhibitors for treatment of **osteoporosis**)

IT 9036-21-9, Phosphodiesterase IV
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibitors; phosphodiesterase IV inhibitors for treatment of **osteoporosis**)

IT 58-55-9, biological studies 2850-36-4 **6493-05-6** 7464-76-8
28822-58-4 29925-17-5 31542-48-0 31542-53-7 31542-62-8
41078-02-8 55242-55-2 57076-71-8 94733-93-4 102146-07-6
118024-67-2 121875-96-5 125573-05-9 131627-58-2 135462-05-4
135462-18-9 135462-19-0 135484-46-7 137002-96-1 137027-45-3
137296-49-2 139093-27-9
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phosphodiesterase IV inhibitors for treatment of **osteoporosis**)

L140 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:365552 HCAPLUS
DN 127:89977
TI Hyperfibrinogenemia and cardiovascular risk: possible strategies for intervention
AU Koenig, W.; Hoffmeister, A.; Hombach, V.
CS Department of Internal Medicine II-Cardiology, University of Ulm Medical Centre, Ulm, D-89081, Germany
SO Fibrinolysis Proteolysis (**1997**), 11(Suppl. 1, Third International Fibrinogen Symposium: Hemostasis, Inflammation and Cardiovascular Disease, 1996), 41-46
CODEN: FBPRFP
PB Churchill Livingstone
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
Section cross-reference(s): 14
AB A review with 68 refs. Elevated plasma fibrinogen has been identified as an independent predictor of cardiovascular diseases. Although abundant evidence suggests a causal role of fibrinogen in the pathogenesis of atherothrombotic complications, this has not yet been proven. To overcome this dilemma, several strategies seem conceivable to intervene with hyperfibrinogenemia. Abstention from smoking and regular long-term endurance exercise significantly decrease fibrinogen. Treatment of chronic infections such as Helicobacter pylori, Chlamydia pneumoniae, or **dental** disease possibly influences cardiovascular risk indirectly by modifying fibrinogen levels. A no. of drugs have been shown to reduce plasma fibrinogen besides their main therapeutic action; clin., fibrates are by far the most important group. Other oral drugs with appreciable fibrinogen-lowering capacity include ticlopidine, **pentoxifylline**, beta-adrenergic blockers, ACE inhibitors, and several steroid hormones. Large clin. trials in patients post-myocardial infarction, with advanced periphenol arterial occlusive disease (POAD), and with diabetes mellitus, are under way, investigating in more detail the possible therapeutic efficacy of lowering fibrinogen on clin. endpoints. Aspirin might influence the phys. properties of the fibrin gel structure, thereby rendering the clot more amenable to endogenous fibrinolysis. Chronic application of low dose urokinase or apheresis may be suitable in selected patient groups. Finally, a new approach consists in the interference with fibrinogen-dependent platelet aggregation through blockade of the glycoprotein IIb/IIIa-receptors.

ST review hyperfibrinogenemia cardiovascular disease treatment

IT Cardiovascular agents

Cardiovascular diseases
(hyperfibrinogenemia and cardiovascular disease risk and possible strategies for intervention in humans and lab. animals)
IT Fibrinogens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(hyperfibrinogenemia and cardiovascular disease risk and possible strategies for intervention in humans and lab. animals)

L140 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:234793 HCAPLUS
DN 124:332958
TI Suppressive effect of N-(benzyloxycarbonyl)-L-phenylalanyl-L-tyrosinal on **bone** resorption in vitro and in vivo
AU Woo, Je-Tae; Yamaguchi, Kohji; Hayama, Takahiro; Kobori, Takeo; Sigeizumi, Sanae; Sugimoto, Kikuo; Kondo, Kiyosi; Tsuji, Tomoko; Ohba, Yasuo; et al.
CS Sagami Chemical Research Center, Nishioonuma 4-4-1, Sagamihara, Kanagawa, 229, Japan
SO Eur. J. Pharmacol. (**1996**), 300(1/2), 131-5
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
CC 1-12 (Pharmacology)
AB The suppressive effect of N-(benzyloxycarbonyl)-L-phenylalanyl-L-tyrosinal on **bone** resorption was examd. in vitro and in vivo. This synthetic **peptidyl aldehyde** was a potent and selective cathepsin L inhibitor in our screening for cysteine protease inhibitors. In the pit formation assay with unfractionated rat **bone** cells, 1.5 nM of this compd. markedly inhibited **parathyroid** hormone-stimulated **osteoclastic bone** resorption. In addn., i.p. administration of this **peptidyl aldehyde** (2.5-10 mg/kg) for 4 wk suppressed **bone** wt. loss dose dependently in the ovariectomized mouse, exptl. model of **osteoporosis**. Hydroxyproline measurement of the decalcified femurs from these ovariectomized mice suggested that this compd. acts as a **bone** resorption suppressor through the inhibition of collagen degrdn.
ST **peptidyl aldehyde bone** resorption cysteine protease
IT Collagens, biological studies
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(suppression of **bone** resorption by (benzyloxycarbonyl)phenylalanyltyrosinal by inhibition of collagen degrdn.)
IT **Bone**
Resorption
(suppressive effect of cysteine protease inhibitor (benzyloxycarbonyl)phenylalanyltyrosinal on **bone** resorption)
IT 167498-29-5
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(suppressive effect of cysteine protease inhibitor (benzyloxycarbonyl)phenylalanyltyrosinal on **bone** resorption)
IT 37353-41-6, Cysteine protease 60616-82-2, Cathepsin L
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(suppressive effect of cysteine protease inhibitor (benzyloxycarbonyl)phenylalanyltyrosinal on **bone** resorption)

L140 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1995:996589 HCAPLUS
DN 124:45676
TI Immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods
IN Mak, Vivien H. W.
PA De Novo Corp, USA
SO PCT Int. Appl., 129 pp.
CODEN: PIXXD2

DT Patent
LA English
IC ICM A61K045-00
ICS C12N015-00; C12N015-09; C12N015-19; C12Q001-00; C12Q001-66; G01N033-53
CC 1-1 (Pharmacology)
Section cross-reference(s): 15, 63
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9527510	A1	19951019	WO 1995-US4677	19950411	<--
	W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT					
	RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	AU 9523857	A1	19951030	AU 1995-23857	19950411	<--
	EP 757558	A1	19970212	EP 1995-917009	19950411	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
	JP 10500669	T2	19980120	JP 1995-526541	19950411	<--
	EP 937460	A2	19990825	EP 1999-201333	19950411	<--
	EP 937460	A3	20000405			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
	US 5962477	A	19991005	US 1998-97441	19980615	<--
	US 6190691	B1	20010220	US 1998-97440	19980615	<--
PRAI	US 1994-225991	A2	19940412	<--		
	US 1994-271287	A	19940706	<--		
	US 1995-400234	A	19950303	<--		
	EP 1995-917009	A3	19950411	<--		
	WO 1995-US4677	W	19950411	<--		
	US 1995-463819	B1	19950605	<--		

AB Screening methods are provided for evaluating compds. capable of suppressing cytokine prodn. either in vitro or in vivo. The methods generally involve stimulating the prodn. of a cytokine in a cell, exposing a portion of the cells to a putative cytokine-modulating agent, and detg. subsequent levels of cytokine prodn. in the cells. Addnl., the present invention provides certain compds. identified by this method, as well as methods for treating conditions modulated by TNF. The methodol. of the invention may be used for e.g. prevention or redn. of transdermal drug delivery system-induced irritation and treatment of skin or systemic inflammatory conditions. Examples include e.g. inhibition of stimulated cytokine prodn. in human cells by a variety of drugs. Verapamil was effective in preventing the development of skin inflammatory responses in mice.

ST inflammation inhibitor immunomodulator screening; cytokine inhibiting agent screening; therapeutic skin systemic inflammation

IT Lymphokines and Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(KC, mRNA for; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Electric field
(cytokine prodn.-modulating; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Ribonucleic acids, messenger
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(for cytokine or MHC class II mol.; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Acquired immune deficiency syndrome
Animal tissue culture
Antidiabetics and Hypoglycemics
Cachexia
Dermatitis
Immunomodulators

Inflammation inhibitors
Lupus erythematosus
Multiple sclerosis
Psoriasis
Therapeutics
Transcription, genetic
Transplant and Transplantation
(immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Allergens
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Diarrhea
(inhibitors; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Iontophoresis
(iontophoretic current, cytokine prodn.-modulating; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Ischemia
(reperfusion; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Gene
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(reporter; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT **Bone**
(resorption; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Ultraviolet radiation
(skin inflammation induced by; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Cosmetics
(skin sensitization or irritation from; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Gene, animal
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(transcription frequency; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Intestine, disease
(Crohn's, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Glycoproteins, specific or class
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(ICAM-1 (intercellular adhesion mol. 1), immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Histocompatibility antigens
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(MHC (major histocompatibility antigen complex), class II, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Respiratory distress syndrome
(adult, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Bronchodilators
(antiasthmatics, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Inflammation inhibitors
(antirheumatics, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

IT Dermatitis
(atopic, immune- and inflammation-modulating cytokine-inhibiting agent

screening and therapeutic methods)
IT Ion channel blockers
(calcium, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Gene
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(chimeric, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Dermatitis
(contact, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Shock
(endotoxin, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Transplant and Transplantation
(graft-vs.-host reaction, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Allergy
(hypersensitivity, contact, allergic; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Eye, disease
(inflammation, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Intestine, disease
(inflammatory, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Lymphokines and Cytokines
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(interleukin 1, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Lymphokines and Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin 10, mRNA; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Lymphokines and Cytokines
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(interleukin 1.alpha., mRNA; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Lymphokines and Cytokines
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(interleukin 1.beta., immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Skin
(keratinocyte, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Diuretics
(loop, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Diuretics
(potassium-sparing, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Perfusion
(re-, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Pharmaceutical dosage forms
(transdermal, skin adverse reaction from; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Lymphokines and Cytokines
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(tumor necrosis factor, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT Adrenergic agonists

(.beta.-, immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT 7440-70-2, Calcium, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study) (channel, blockers; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT 56-75-7, Chloramphenicol 9014-00-0, Luciferase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (gene; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT 50-35-1, Thalidomide 50-52-2, Thioridazine 51-41-2, Arterenol 52-01-7, Spironolactone 52-53-9, Verapamil 54-31-9, Furosemide 915-30-0, Diphenoxylate 1143-38-0, Dithranol 1214-79-5 1845-11-0, Nafoxidine 2062-78-4, Pimozide 2609-46-3, Amiloride **6493-05-6**, **Pentoxifylline** 10540-29-1, Tamoxifen 21829-25-4, Nifedipine 23031-25-6, Terbutaline 29925-17-5, RO 20-1724 36622-29-4, (-)-Verapamil 38321-02-7, (+)-Verapamil 42399-41-7, Diltiazem 52468-60-7, Flunarizine 53179-11-6, Loperamide 55985-32-5, Nicardipine 64706-54-3, Bepridil 66085-59-4, Nimodipine 75695-93-1, Isradipine 100427-26-7, Rec 15/2375
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT 58-94-6D, Thiazide, derivs. 140-29-4D, Benzeneacetonitrile, derivs. 27790-75-6D, Dihydropyridine, derivs. 73087-48-6D, 1,5-Benzothiazepin-4(5H)-one, derivs.
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT 9025-82-5, Phosphodiesterase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)
IT 302-79-4, Retin-A
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (skin inflammation from; immune- and inflammation-modulating cytokine-inhibiting agent screening and therapeutic methods)

L140 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:99328 HCAPLUS
DN 116:99328
TI Method for treating equine navicular disease with **pentoxifylline**, and composition containing **pentoxifylline** for administrating to horses
IN Drizen, Alan
PA Hyal Pharmaceutical Corp., Can.
SO U.S., 9 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A01N043-90
NCL 514261000
CC 1-8 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5077296	A	19911231	US 1987-128175	19871203 <--

AB Equine navicular disease is treated with a compn. contg. **pentoxifylline** (I) in a daily dose of 6-30 g to alleviate lameness. Preferably the compn. comprises I 7.2, confectioners' sugar 8.5, corn sugar 83.895, colloidal SiO2 0.247, and artificial color 0.158 wt.%. Horses were treated orally with I.
ST horse navicular **bone** disease **pentoxifylline**
IT Horse

(navicular disease treatment in, **pentoxifylline** for)
IT Pharmaceutical dosage forms
(of **pentoxifylline**, for navicular disease treatment in horse)
IT **Bone**
(navicular, treatment of, of horse, with **pentoxifylline**)
IT Pharmaceutical dosage forms
(oral, of **pentoxifylline**, for navicular disease treatment in horse)
IT **6493-05-6, Pentoxifylline**
RL: BIOL (Biological study)
(navicular disease in horse treatment with)

=> fil wpix
FILE 'WPIX' ENTERED AT 17:37:36 ON 01 MAR 2002
COPYRIGHT (C) 2002 DERWENT INFORMATION LTD

FILE LAST UPDATED: 26 FEB 2002 <20020226/UP>
MOST RECENT DERWENT UPDATE 200213 <200213/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> SDI'S MAY BE RUN ON EVERY UPDATE OR MONTHLY AS OF JUNE 2001.
(EVERY UPDATE IS THE DEFAULT). FOR PRICING INFORMATION
SEE HELP COST <<<

>>> FOR UP-TO-DATE INFORMATION ABOUT THE DERWENT CHEMISTRY
RESOURCE, PLEASE VISIT
http://www.derwent.com/chemistryresource/index.html <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

=> d all abeq tech tot

L155 ANSWER 1 OF 5 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN **2000-171065** [15] WPIX
DNC **C2000-053186**
TI Compound that inhibits the activity of NF-kappa B useful for enhancing bone formation.
DC B04 B05
IN GARRETT, I R; MUNDY, G R; ROSSINI, G
PA (OSTE-N) OSTEOSCREEN; (OSTE-N) OSTEOSCREEN INC
CYC 73
PI WO 2000002548 A2 20000120 (200015)* EN 37p A61K031-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AU BA BB BG BR CA CN CU CZ EE GE HU IL IN IS JP KP KR LC LK LR LT LV MD MG MK MN MX NO NZ PL RO SD SG SI SK TR TT US UZ VN
AU 9963109 A 20000201 (200028) A61K031-00
EP 1096924 A1 20010509 (200128) EN A61K031-00
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
ADT WO 2000002548 A2 WO 1999-US15533 19990709; AU 9963109 A AU 1999-63109 19990709; EP 1096924 A1 EP 1999-933827 19990709, WO 1999-US15533 19990709
FDT AU 9963109 A Based on WO 200002548; EP 1096924 A1 Based on WO 200002548
PRAI US 1998-113947 19980710
IC ICM A61K031-00
AB WO 200002548 A UPAB: 20000323
NOVELTY - Enhancing bone formation, treating pathological dental conditions, treating degenerative joint conditions by administration of NF-kappa B inhibitor.
DETAILED DESCRIPTION - Enhancing bone formation or treating pathological dental conditions or treating degenerative joint conditions in a vertebrate animal comprises administration of a compound that inhibits the activity of NF-kB or that inhibits proteasomal activity or that inhibits production of proteasome proteins.

INDEPENDENT CLAIMS are included for the following:
(1) treatment of a condition benefited by stimulating hair growth comprising administration of a compound that inhibits the activity of NF-kB or that inhibits proteasomal activity or that inhibits production of these proteins, and
(2) identifying a compound which enhances bone growth or stimulates hair growth comprising subjecting a candidate compound to an assay to assess its ability to inhibit:
(a) NF-kB activity, or
(b) the production of NF-kB, or
(c) proteasomal activity, or
(d) the production of enzymes with proteasomal activity, where for all the inhibitory compound is identified as a compound that enhances bone growth.
ACTIVITY - Osteopathic; Endocrine-Gen.; Screening; Vulnerary. PSI (N-carbobenzoyl-Ile-Glu-(OtBu)-Ala-Leu-CHO) was assayed in vitro for calvarial bone growth. Administered at 0.1, 1 and 5 mg/kg/day, the % increase in bone area compared to control was 21.7, 35.4 and 32.1%, respectively. The 1 and 5 mg/kg/day doses produced an increase in new bone width of 19.9%.
MECHANISM OF ACTION - Antimetastatic; Nuclear-Factor-Inhibitor-Kappa-B.
USE - The method can be used for enhancing bone formation, treating pathological dental conditions, degenerative bone conditions, osteoporosis, bone fracture or deficiency, primary or secondary hyperparathyroidism, periodontal disease or defect, metastatic bone disease, osteolytic bone disease, post-plastic surgery, post-prosthetic joint surgery, and post-dental implantation, and for stimulating hair growth (claimed). The compounds may also be useful in wound healing or tissue repair.
ADVANTAGE - None given.
Dwg.0/1

FS CPI
FA AB; DCN
MC CPI: B04-C01; B06-D13; B06-F05; B07-A02B; B07-D03; B10-A06; B10-A10; B10-D02; B11-C08; B12-K04A; B14-D03; **B14-N01**; B14-N06; B14-N11; B14-N17B; B14-R02
TECH UPTX: 20000323
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Method: The compound does not inhibit the isoprenoid pathway. The compound is **lactacystin**, a peptidyl aldehyde or PTX. The method further comprises administration of one or more agents that promote bone growth or that inhibit bone resorption such as bone morphogenetic factors, anti-resorptive agents, osteogenic factors, cartilage-derived morphogenetic proteins, growth hormones, estrogens, bis phosphonates, statins or differentiating factors.

L155 ANSWER 2 OF 5 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN **2000-146446** [13] WPIX
DNN **N2000-108408** DNC **C2000-045745**
TI Inhibiting cytokine-mediated bone resorption in a human patient comprises administering a pharmaceutical comprising, e.g. ciprofloxacin, **pentoxifylline** or isobutylmethyl xanthine.
DC B05 B07 D22 P32
IN O'KEEFE, R J; ROSIER, R N
PA (UYRP) UNIV ROCHESTER
CYC 1
PI US 6010711 A 20000104 (200013)* 7p A61F002-28
ADT US 6010711 A US 1996-592123 19960126
PRAI US 1996-592123 19960126
IC ICM A61F002-28
ICS A61F002-00
AB US 6010711 A UPAB: 20000313
NOVELTY - A method of inhibiting cytokine-mediated bone resorption in a human patient comprises administering a cytokine-mediated bone resorption inhibiting active agent selected from ciprofloxacin, **pentoxifylline**, isobutylmethyl xanthine, rolipram and terferol in

a pharmaceutical carrier.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a therapeutic composition comprising:
(a) an article selected from a bone cement constituent and an orthopedic prosthesis constituent;
(b) a cytokine-mediated bone resorption inhibiting active agent as described above.
USE - No further details.
Dwg.0/2

FS CPI GMPI
FA AB; DCN
MC CPI: B04-A06; B06-D02; B06-D09; B07-D03; B10-E02; **B14-N01**; D09-C01
TECH UPTX: 20000313
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred materials: The cytokine-mediated bone resorption inhibiting active agent is coated onto the carrier, or incorporated in the carrier by means of a controlled release matrix. The controlled release matrix containing the active agent includes capsules, especially microcapsules. The active agent is present at 0.001-0.1 wt.%.

L155 ANSWER 3 OF 5 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN **1995-132087** [18] WPIX
DNC **C1995-060906**
TI Chewable tablets for treatment of, e.g. osteoporosis - contg. microparticles with retard properties.
DC A96 B07
IN KORSATKO, B; KORSATKO, W; TRITTHART, W
PA (KORS-I) KORSATKO W
CYC 31
PI DE 4333190 A1 19950330 (199518)* 10p A61K009-22
WO 9508988 A1 19950406 (199519) DE 30p A61K009-20
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA CN CZ FI HU JP KR NO PL RU SK UA US
AU 9478088 A 19950418 (199531) A61K009-20
DE 4333190 C2 19960530 (199626) 10p A61K009-22
EP 715515 A1 19960612 (199628) DE A61K009-20
R: AT BE CH DE ES FR GB IT LI NL PT
ADT DE 4333190 A1 DE 1993-4333190 19930929; WO 9508988 A1 WO 1994-EP3166 19940922; AU 9478088 A AU 1994-78088 19940922; DE 4333190 C2 DE 1993-4333190 19930929; EP 715515 A1 EP 1994-928795 19940922, WO 1994-EP3166 19940922
FDT AU 9478088 A Based on WO 9508988; EP 715515 A1 Based on WO 9508988
PRAI DE 1993-4333190 19930929
IC ICM A61K009-20; A61K009-22
ICS A61K033-06; A61K033-16
AB DE 4333190 A UPAB: 19950518
Chewable tablet comprises a conventional chewable mass which contains microparticles (which contain an active agent) with retard properties. Due to the elasticity and strength of the microparticles, they are not destroyed during the chewing process.
Pref. the microparticles are composed of a retarding, elastic, active agent-contg. matrix (e.g. of Eudragit (RTM) derivs. and/or cellulose derivs.) and a retarding (and opt. elastic) coat (of, e.g., polyacrylates and/or cellulose derivs.).
USE - The tablets give delayed/sustained release of active agent e.g. cpds. for treatment of osteoporosis, vasodilators, antiphlogistics, antirheumatics, H2 blockers, antiallergic agents, antihypertensives, or diuretics.
Dwg.0/2

FS CPI
FA AB; DCN
MC CPI: A12-V01; B04-C02A; B04-C03B; B05-B02A3; B12-M10; B12-M11; **B14-N01**

L155 ANSWER 4 OF 5 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN **1992-032705** [04] WPIX
DNC **C1992-014274**
TI Equine navicular disease treatment, for prevention of lameness - using **pentoxifylline** and opt. sugar carrier with improved relief over prior art.
DC B02 C02
IN DRIZEN, A
PA (HYAL-N) HYAL PHARM CORP
CYC 1
PI US 5077296 A 19911231 (199204)*
ADT US 5077296 A US 1987-128175 19871203
PRAI US 1987-128175 19871203
IC A01N043-90
AB US 5077296 A UPAB: 19931006
Treatment comprises administering a compsn, contg. **pentoxifyllin** (P) in a daily dose of 6-30 g and opt. sugar to alleviate lameness obtd. from ND.
USE/ADVANTAGE - Counteracts pathogenetic mechanism of tissue hypoxia and improved open prior art treatments giving symptomatic relief only. Also applied in laminitis a life threatening condition in which systemic toxicity results in ischaemia of the sensitive laminae in the foot with eventual sepn of the hoof wall from its supporting structures.
0/0
FS CPI
FA AB; DCN
MC CPI: B04-A06; **B12-J08**; B12-L09; C04-A06; **C12-J08**; C12-L09

L155 ANSWER 5 OF 5 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN **1989-014862** [02] WPIX
DNN **N1989-011243** DNC **C1989-006962**
TI Treatment of stomatitis - by electrophoretic morning administration of heparin to spina linguae, and treatment with specified drug, glutamic acid and phytin.
DC B05 P34
IN GRINBERG, L M; MAKAROV, V A; PEREGUDOVA, G N
PA (HAEM-R) HAEMATOLOGY BLOOD TRANSF; (MOME-R) MOSC MED STOMATOL
CYC 1
PI SU 1407492 A 19880707 (198902)* 2p
ADT SU 1407492 A SU 1986-4110242 19860905
PRAI SU 1986-4110242 19860905
IC A61K031-00; A61N001-30
AB SU 1407492 A UPAB: 19930923
Stomatatis is treated more efficiently as follows. The patient is given, in the early hours, heparin electrophoretically, using a current of negative polarity, at the spina linguae, and this is supplemented by the following additional treatment: 0.025g of Trental (RTM, **pentoxiphylline**) 3 times a day, 0.5g of glutamic acid 4 times a day, and 0.25g phytin 4 times a day. Improvement occurs within 10-14 days, and remission time is increased to 5-7 months.
ADVANTAGE - Shorter time of treatment, extended time of remission.
Bul.25/7.7.88.
0/0
FS CPI GMPI
FA AB; DCN
MC CPI: B04-A06; B04-C02E1; B05-A01B; B05-B01P; B10-B02J; B12-D07; B12-L04

=> d his

(FILE 'HOME' ENTERED AT 15:53:40 ON 01 MAR 2002)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 15:53:50 ON 01 MAR 2002
L1 3 S 6493-05-6 OR 134381-21-8 OR 133343-34-7
L2 16 S (6493-05-6 OR 134381-21-8 OR 133343-34-7)/CRN

```
L3            3 S L2 NOT MXS/CI
L4            1 S L3 AND CLH
L5            1 S 140879-24-9

     FILE 'MEDLINE' ENTERED AT 15:55:08 ON 01 MAR 2002
L6         2763 S L1
L7            0 S L4
                E LACTACYSTIN
L8          549 S E2-E5
                E EPOXOMICIN
L9           17 S E3,E4
                E PENTOXYFIL
L10          63 S  E2,E4-E8,E10,E11
                E EPNTOIFIL
                E PENTOIFIL
                E PENTOXIFIL
L11        2812 S E4-E19,E21,E23-E26
                E PENTOXYPHIL
L12          39 S  E4-E8
                E PENTOXIPHIL
L13          40 S E4-E7
L14        3403 S L6-L13
L15           9 S L14 AND DENTAL?/FS
L16          57 S L14 AND (A14.254. OR A12.300. OR A12.383. OR G10.549. OR C7.
                E BONE/CT
L17          14 S E9+NT AND L14
L18           0 S E156+NT AND L14
L19           0 S E178+NT AND L14
L20           1 S E185+NT AND L14
L21           8 S E204+NT AND L14
L22           0 S E353+NT AND L14
L23           0 S E572+NT AND L14
L24           2 S E606+NT AND L14
L25           0 S E716+NT AND L14
L26           4 S E724+NT AND L14
L27           3 S E733+NT AND L14
L28           1 S E789+NT AND L14
L29           0 S E812+NT AND L14
                E OSTEOPOROSIS/CT
L30           2 S E3+NT AND L14
                E OSTEOBLAST/CT
L31           5 S E26+NT AND L14
L32           2 S E223+NT AND L14
L33           0 S E247+NT AND L14
                E HYPERPARATHYROIDISM/CT
L34           0 S E3+NT AND L14
                E JOINT/CT
L35          20 S E64+NT AND L14
L36           0 S E113+NT AND L14
L37           1 S E168+NT AND L14
L38           2 S E231+NT AND L14
L39          68 S SU/CT AND L14
L40         251 S E4./CT AND L14
L41           0 S L40 AND E4.545.550./CT
L42           9 S L40 AND E4.555./CT
L43           2 S L40 AND E4.650./CT
L44           0 S L5
L45        3755 S ?PROTEASOM?
L46         508 S L14 AND L45
L47           6 S L46 AND L15-L39,L41-L44
L48         171 S L15-L39,L41-L44
L49         114 S L48 AND PY<=1998
L50          37 S L49 NOT AB/FA
L51          77 S L49 NOT L50
                SEL DN AN 61 65 70 71 L51
L52           4 S L51 AND E1-E12
```

```
L53          57 S L48 NOT L49
                SEL DN AN 20 27 37
L54           3 S L53 AND E13-E21
                E PROSTHESIS/CT
L55           2 S L14 AND (E19+NT OR E35+NT OR E59+NT)
                E E3+ALL
L56          14 S E2+NT AND L14
                E IMPLANT/CT
                E E53+ALL
                E IMPLANTS/CT
L57          16 S L55-L56
                SEL DN AN 1 3 5
L58           3 S L57 AND E1-E9
L59           9 S L52,L54,L58
L60           9 S L59 AND L6-L59
                E PARATHYROID/CT
L61           0 S E8+NT AND L14
L62           0 S E40+NT AND L14
L63           3 S E74+NT AND L14
L64           2 S L63 AND L15-L39,L42-L60 NOT KIDNEY/CT
L65          10 S L60,L64

     FILE 'REGISTRY' ENTERED AT 16:44:45 ON 01 MAR 2002

     FILE 'MEDLINE' ENTERED AT 16:45:20 ON 01 MAR 2002
L66           0 S L14 AND (MUNDY ? OR GARRETT ? OR ROSSINI G?)/AU

     FILE 'BIOSIS' ENTERED AT 16:46:23 ON 01 MAR 2002
L67        3661 S L14
                E EPOXOMICIN
L68          14 S E3,E4
                E LACTACYSTIN
L69         532 S E3-E5
                E PENTOXIFIL
L70        2874 S E4-E24
L71          80 S E40-E42,E45,E46,E48
L72          56 S E63-E67
L73        3664 S L67-L72
L74         129 S L73 AND (BONE OR OSTEO? OR OESTEO? OR JOINT OR DENTAL OR DENT
L75          73 S L73 AND 19?/CC
L76          78 S L73 AND 22012/CC
L77         128 S L73 AND 1800?/CC
L78           0 S L73 AND 17010/CC
L79         198 S L73 AND 22016/CC
L80         405 S L73 AND 240?/CC
L81         222 S L73 AND (11105 OR 11107)/CC
L82          68 S L81 AND L74-L80
L83          80 S L74,L75,L76,L79 AND L77
L84          67 S L83 NOT L82
L85           6 S L84 AND (LINEAGE OR LONG BONE OR DIFFERENTIATION OR BONE MORP
L86           1 S L84 AND ANTIOSTEO?/TI
L87           7 S L85,L86
L88         349 S L74-L77,L79 NOT L82-L87
L89         317 S L88 AND PY<=1999
L90        1112 S L73 AND 00520/CC
L91        1295 S L73 AND (CONGRESS OR CONFERENCE OR POSTER OR SYMPOS? OR MEETI
L92         217 S L91 NOT CONFERENCE/DT
L93         122 S L92 NOT ARTICLE/DT
L94          94 S L93 NOT GENERAL REVIEW/DT
L95        1078 S L91 NOT L92,L93
L96        1172 S L94,L95
L97          63 S L96 AND L74,L75,L76
L98          49 S L96 AND L77
L99          65 S L96 AND L79
L100        131 S L96 AND L80
L101         84 S L96 AND L81
```

```
L102         312 S L97-L101
L103         266 S L102 NOT L82-L87
L104           7 S L87 AND L67-L103
L105           1 S L73 AND (MUNDY ? OR GARRETT ? OR ROSSINI ?)/AU
L106           8 S L104,L105 AND L67-L105

     FILE 'BIOSIS' ENTERED AT 17:16:50 ON 01 MAR 2002

     FILE 'HCAPLUS' ENTERED AT 17:17:05 ON 01 MAR 2002
L107        2629 S L73
                 E LACTACYSTIN
L108         550 S E3,E5,E6
                 E EPOXOMICIN
L109          21 S E3,E4
                 E PENTOXIFIL
L110        1748 S E2-E29,E33
L111         102 S E99-E102
L112          13 S E140-E142,E148,E140
L113         131 S PEPTIDYL(L)ALDEHYDE
L114        2758 S L107-L113
                 E BONE/CT
                 E E3+ALL
L115          81 S L114 AND E9,E3+NT
L116          45 S L114 AND (E56+NT OR E58+NT OR E59+NT)
                 E E58+ALL
L117          42 S L114 AND E3+NT
                 E TOOTH/CT
                 E E3+ALL
L118           1 S L114 AND E9,E8+NT
L119           0 S L114 AND E27+NT
                 E E7+ALL
L120           6 S L114 AND E39-E47
L121          82 S L114 AND (BONE OR OESTEO? OR OSTEO? OR TOOTH OR TEETH OR DENT
                 E PROSTHE/CT
                 E E18+ALL
L122           0 S L114 AND E1
L123           5 S L114 AND E2+NT
                 E IMPLANTATION/CT
                 E E11+ALL
L124           2 S L114 AND E2
L125           2 S L114 AND (MUNDY ? OR GARRETT ? OR ROSSINI G?)/AU
L126           2 S L114 AND OSTEOSCREEN?/PA,CS
L127         155 S L115-L126
L128          95 S L127 AND (PY<=1998 OR PRY<=1998 OR AY<=1998)
L129          14 S L128 AND (L5 OR ?PROTEASOM?)
L130          15 S L125,L126,L129
L131           6 S L130 AND (BONE OR OSTEO? OR PARATHYROID?)
L132           4 S L131 NOT (RENAL OR PROTEASE)/TI
L133           4 S L125,L126,L132
L134          81 S L128 NOT L129-L133
L135          16 S L134 AND BONE#/CW
L136           5 S L135 NOT MARROW
L137           9 S L133,L136
L138           2 S L134 AND DENT?
L139           1 S L134 AND (TOOTH OR TEETH)
L140          11 S L137-L139

     FILE 'HCAPLUS' ENTERED AT 17:31:08 ON 01 MAR 2002

     FILE 'WPIX' ENTERED AT 17:31:33 ON 01 MAR 2002
L141         128 S LACTACYSTIN? OR EPOXOMICIN? OR EPOXOMYCIN? OR PENTOXIFILLIN?
                 E LACTACYSTIN/DCN
                 E EPOXOMICIN/DCN
                 E PENTOXYFILLIN/DCN
                 E E2+ALL
L142          96 S E2
```

```
                E LACTACYSTIN
L143         16 S E3
                E EPOXOMICIN
                E PENTOXIFIL
L144         98 S E4-E11
L145          1 S E1
L146          7 S E13-E16
L147         18 S E35-E38
L148         42 S E45-E52
                E PENTOXYFIL
L149        218 S L141-L148
L150          4 S L149 AND (P910 OR P911 OR P912 OR P913 OR P923)/MO,M1,M2,M3,M
L151          0 S L149 AND (A12-V02B OR A12-V04B OR B12-L03 OR C12-L03 OR D08-A
                E A61K007-16/IC,ICM,ICS
L152          0 S L149 AND E3-E39
L153          5 S L149 AND (B12-J08 OR C12-J08 OR B14-N01 OR C14-N01)/MC
L154          8 S L150,L153
                SEL DN AN 4-8
L155          5 S L154 AND E1-E12

     FILE 'WPIX' ENTERED AT 17:37:36 ON 01 MAR 2002
```